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Role of concurrent transcervical resection and curettage (TCR+C) in detecting endometrial cancer

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Summary

Objectives: The aim of this study was to evaluate the usefulness of concurrent transcervical resection and total curettage (TCR+C) for patients in whom a definitive preoperative pathological diagnosis of the presence or absence of endometrial cancer (EC) could not be obtained. *Materials and Methods:* A total of 125 patients who underwent curettage with office hysteroscopy (63 patients) or TCR+C (62 patients) for suspected uterine malignancy were retrospectively reviewed by focusing on pathologic and hysteroscopic findings. Furthermore, the pathological diagnostic accuracies of EC between curettage alone and TCR+C were analyzed in 29 EC patients who received hysterectomy. *Results:* Six of 12 suspected EC patients (50%) who underwent curettage alone had a discrepancy in the final diagnosis by hysterectomy; meanwhile, 15 of 17 suspected EC patients (88.2%) were accurately diagnosed as EC by TCR+C before hysterectomy. In total, TCR+C provided significantly more accurate pathological diagnosis of EC than curettage alone with office hysteroscopy (p = 0.038 by Fisher's exact test). In addition, hysteroscopic findings showed that all resected specimens of white desquamation lesions with atypical branched vessels in the endometrium were diagnosed as endometrial cancer. No significant adverse effect was observed in TCR+C group. *Conclusions:* Endometrial diagnosis with TCR+C is a more useful technique for suspected EC lesions than curettage alone.

Key words: Atypical hyperplasia; Endometrial cancer; Transcervical resection; Hysteroscopy; Total curettage.

Introduction

Endometrial cancer (EC) is the prevalent type of gynecologic malignancy of the genital tract [1]. The Federation of Gynecology and Obstetrics (FIGO) Stage is the independent variable that is best related to prognosis [2]. Over the past few decades, the incidence has been increasing in developed countries, including Japan, but its prognosis is generally favorable, with a five-year survival rate of about 80-90% in the early stages [3, 4]. The majority of ECs confined to the uterus are identified at the initial stages, and a differential diagnosis between atypical endometrial hyperplasia (AEH) and EC is of great clinical relevance [2, 5]. Preoperative diagnosis of endometrial malignancy by conventional cytology has been reported to be lower than cervical examination to diagnose cytologic atypia in the glandular endometrium [6]. Pelvic sonography may also be performed to evaluate other etiologies of abnormal uterine bleeding or to assess endometrial thickness in postmenopausal women [7]. Ultrasound findings, however, sometimes do not correlate with the sensitivity of outpatient endometrial sampling cytology with conventional biopsy in patients when multiple endometrial polyps or submucosal myomas co-exist in the uterine cavity [8]. Therefore, the distinction between AEH and EC using an endometrial biopsy specimen obtained by dilation of the cervix and endometrial curettage is still the gold standard method for endometrial assessment [9], but it continues to present a difficult preoperative differential diagnosis because of the frequent underestimation of concurrent infiltrating carcinoma found in the hysterectomy specimens in 40% to 60% of patients [5, 10, 11]. Atypical hyperplasia is characterized by glandular proliferation with atypical cells, while simple or complex hyperplasia is characterized by cell proliferation without atypia [12]. However, approximately 40% of patients diagnosed with AEH are reported to have concurrent adenocarcinoma in the same specimen [6], and the remaining 70% have a very high risk of cancer development [13, 14]. In addition, approximately 80% of ECs are endometrioid carcinomas with minimal myometrial invasion that arise from atypical complex hyperplasia [15].

In contrast to fractional assessments of endometrial features, office hysteroscopic inspection has been performed to evaluate the entire area of the endometrium by a combined pathological diagnosis. To avoid missing suspicious lesions of blind dilatation and curettage, the current standard procedure for office hysteroscopic visual investiga-

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Table 1. — *Patient and treatment characteristics by TCR+C or total curettage alone*

	N. TCR+C patients (n=62)		N. curettage alone patients (n=63)	
Age, median (range), years	49 (range 27-82)		55 y (range 34-80)	
Endometrial thickening (≥ 10 mm)	41 (68%)		38 (60%)	
Em polyp and/or submucosal leiomyoma	30 (50%)		8 (13%)	
BMI, median (range), kg/m^2	25.6 (range 18-36)		29.2 (range 17-39)	
Number of hysterectomies	30 (48%)		29 (46%)	
Endometrial cytology				
Negative	38		29	n.s.
Suspicious	13		24	n.s.
Positive	11		10	n.s.
Endometrial blind biopsy				
Unsuccessful procedure	2	(3.2%)	2	(3.2%)
Negative	19	(30.6%)	18	(28.6%)
Atypical glands	14	(22.6%)	8	(12.7%)
Endometrial hyperplasia simple	3	(4.8%)	0	(0%)
Endometrial hyperplasia complex	1	(1.6%)	0	(0%)
Atypical polypoidadenomyoma suspected	3*	(4.8%)	0	(0%)
Atypical endometrial hyperplasia complex	15	(24.2%)	31	(49.2%)
Endometrial carcinoma suspected	4	(6.5%)	4	(6.3%)
Endometrial stromal sarcoma suspected	1	(1.6%)	0	(0%)

TCR+C: transcervical resection in combination with curettage
** APAM+AEH susp. one case, APAM+EC susp. one case included in the cases.*
APAM: atypical polypoidadenomyoma, AEMHc: atypical endometrial hyperplasia complex, EC: endometrial cancer, BMI: body mass index.

tion improves the accuracy of diagnosis of focal hyperplasia or EC [16, 17]. It has also been reported that office hysteroscopy has a high success rate for evaluation with lower cost and greater diagnostic accuracy [5, 17-19]. Furthermore, office hysteroscopy with endometrial biopsy is useful to rule out endometrial cancer in postmenopausal women [20]. Nevertheless, even combined use of hysteroscopic inspection with total curettage is still insufficient for detecting localized EC [21]. In addition, patients may suffer pain associated with liquid distension medium to investigate the uterine cavity and the insertion of an office hysteroscope at the time of examination.

For these reasons, the use of transcervical resection (TCR) is considered as a useful procedure performed with a larger angle of view than office hysteroscopy under general anesthesia in the operating room. Recently, the usefulness of TCR under general anesthesia has been reported for the management of myometrial invasion of suspicious endometrial malignant lesions, including atypical polypoid adenomyomas [22]. However, there is still little information related to the usefulness of TCR for differential diagnosis between endometrial cancer and atypical hyperplasia.

The objectives of this study were to retrospectively evaluate the usefulness of TCR in combination with curettage (TCR+C) instead of curettage alone for the differential pathological diagnosis of suspicious EC lesions and to investigate the visual patterns of hysteroscopic imaging findings to efficiently resect focal EC under visual observation.

Materials and Methods

Basic clinical background and histologic data of the 125 patients studied are presented in Table 1. All hysteroscopic reports of patients in whom cytological atypia was detected by cytology with conventional endometrial biopsy at the University of Tokyo Hospital from 2004 to 2015 were reviewed. The study was performed with the written, informed consent of all patients in accordance with the ethical guidelines at the University of Tokyo Hospital. All patients with suspicious results on endometrial pathological screening tests underwent preoperative evaluation, including blood testing for elevated tumor markers (CA125, CEA, CA19-9, etc.), transvaginal and transabdominal ultrasound examinations, computed tomography (CT) scanning, and contrast-enhanced magnetic resonance imaging (MRI). Outpatient hysteroscopy with a 3.5-mm diagnostic hysteroscope HYF type V was performed with no systemic analgesia. Normal saline solution was used as a liquid distension medium, and it was delivered by instillation, setting endouterine pressure to approximately 100 mmHg. All examinations were performed with video imaging under transcervical sonography assist. All procedures were performed by the same skilled hysteroscopic specialist.

Imaging findings in the uterine cavity have been previously reported and are summarized in Figure 1, according to previously published criteria [23]. In the present hospital, the following were considered abnormal findings: 1) atypical vessels;, 2) unevenness of surface contours (nodular, polypoid, papillary protruding lesions), 3) necrosis, 4) irregular surface (coarseness), 5) atrophy, and 6) white desquamation (or opacity).

TCR+C was performed in 62 patients with suspected malignancy based on endometrial fractional biopsy and imaging after outpatient hysteroscopy in the present hospital. The patients were admitted to hospital one day prior to surgery for cervical preparation to dilate the cervical canal by an osmotic dilator to facili-

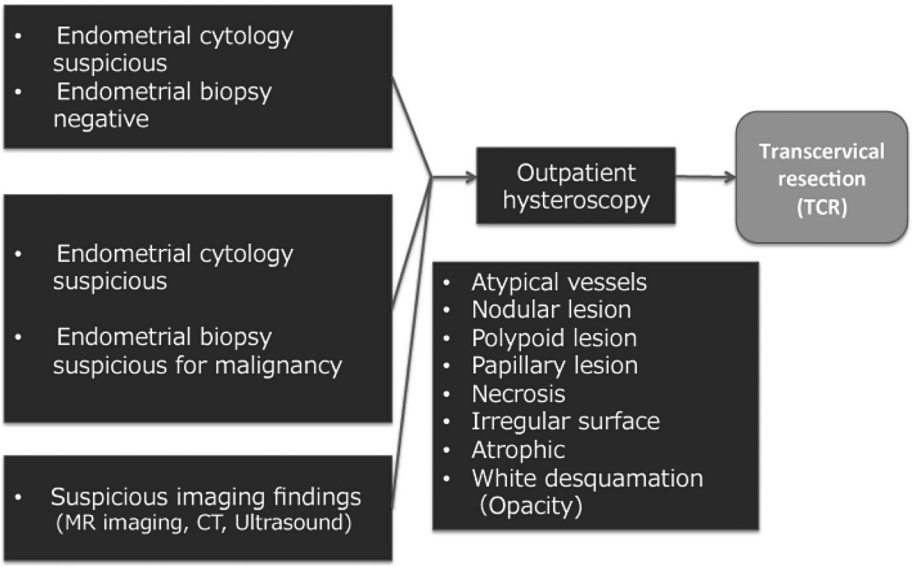

Figure 1. — Management of suspected endometrial malignant lesions In our hospital, transcervical resection (TCR) and total curettage were performed to obtain an accurate differential diagnosis for patients with suspected malignancy based on endometrial fractional curettage with cytology and imaging after outpatient hysteroscopy.

tate resectoscope insertion. With the patient under general anesthesia, the cervical canal was further dilated using a Hegar dilator, and then TCR was carried out using a resectoscope with continuous flow. A uromatic S irrigation solution was used for the hysteroscopic procedure. Any focally growing lesion in the uterine cavity was identified by the expert hysteroscopists, and resection was performed widely to remove all suspected lesions in the uterine cavity. The hysteroscope was then removed, and total curettage was carried out with forceps. After this, the hysteroscope was re-inserted into the uterine cavity, and any localized lesion still left in the cavity was removed under hysteroscopic control. If the endometrial curettage was very scant, a piece of the suspicious region was resected even when no focal lesion had been detected in the cavity. Any tissues resected by TCR+C from the uterine cavity were placed in separate containers with 10% formaldehyde and sent for separate histological analysis by the pathologists.

After the surgery, the final diagnosis was made on the pathological diagnosis of the resected specimen, any curetted fragments, and the hysterectomy specimen depending on the circumstances. If the diagnosis differed between the specimens, the final decision was considered the pathological diagnosis from the hysterectomy specimens.

Standard statistical analyses were performed. Various hysteroscopy findings were analyzed for the accuracy of histological pathologic assessment by TCR+C. Fisher's exact test was used to compare the accuracy of diagnosis between patients who underwent TCR+C and those who underwent total curettage. All statistical tests were two-tailed, and differences were considered significant at $p < 0.05$. JMP-Pro version 10.0.2 software was used for the statistical analyses.

Results

First, the usefulness of TCR+C for differential diagnosis of suspected endometrial malignant lesions was compared to that of total curettage alone. All 125 patients were preoperatively evaluated by endometrial cytology and fractional biopsy under transvaginal ultrasound examination, CT scanning, and MRI, and a definitive pathological diagnosis by examination of biopsied specimens was not obtained in any of the patients. All patients underwent office hysteroscopy because the pathological findings were suspicious for malignancy. As shown in Table 1, all patients were ultimately negative or suspicious for endometrial cytology and fractional biopsy. A discrepancy between cytological and histopathological results may be due to false readings in the presence of several conditions of the endometrial cavity, including the presence of endometrial polyps and/or submucosal leiomyomas.

Among the 62 TCR+C patients in whom a definitive clinicopathological diagnosis could not be obtained from the preoperative examinations, four atypical polypoid adenomyoma (APAM) cases, 18 AEH cases, and 21 EC cases were successfully detected by TCR+C, even with false-negative pathological findings (Table 2), but two cases of AEH were finally diagnosed as EC after hysterectomy. In comparison with TCR+C patients, patients who underwent total curettage alone with office hysteroscopy were diagnosed as AEH, EC or with no malignancy. Therefore, whether TCR+C could contribute more to the differential diagnosis between AEH and EC than total curettage alone among patients who underwent curative hysterectomy was then evaluated. To do this, 12 total curettage cases and 17 TCR+C cases were analyzed. As shown in Table 3, in six patients (50%) it was not possible to discriminate malignant potential by total curettage alone, and there was a discrepancy in the pathological diagnosis of EC after hysterectomy. More-

Table 2. — *Pathological diagnoses made on the basis of TCR+C*

Final diagnosis	Cases (n=62)
Endometrial hyperplasia simple	**1**
Atypical endometrial hyperplasia complex	**18**[#]
Endometrial cancer (endometrioid 20, mucinous 1)	**21**
IA	19
IB	2
Atypical polypoidadenomyoma	**4**
with atypical endometrial hyperplasia complex	1
with endometrial cancer	1
No malignancy (atypical glands included)	**18**
Total	**62**

TCR+C: transcervical resection in combination with curettage.
[#] *Two cases were eventually diagnosed as EC after hysterectomy.*

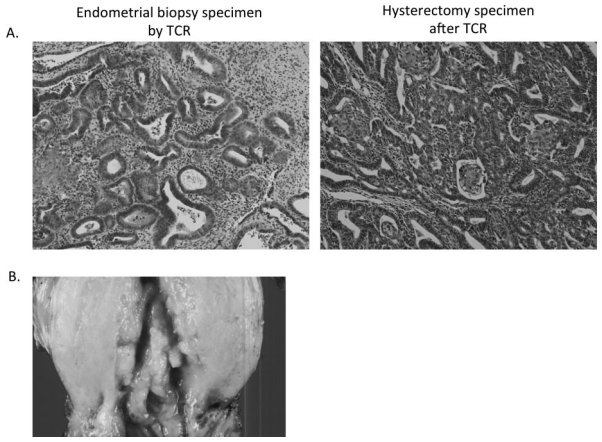

Figure 2. — (A) Microscopic imaging of a patient diagnosed as having AEH with concurrent EC (left). The microscopic pathological findings of the resected specimens by TCR (right). The microscopic pathological findings of the hysterectomy specimen after TCR+C. Back-to-back glands are observed with stromal disappearance in the hysterectomy specimen. (B) Macroscopically, tumor masses are composed of polypoid-like tumor diffusedly arranged in the uterine cavity.

Table 3. — *Comparison of pathological accuracy for EC between TCR+C and total curettage alone (C).*

		Final pathological diagnosis of EC after hysterectomy	
		True	False
C	(n=12)	6	6
TCR+C	(n=17)	15	2
Total		21	8

Fisher's exact test, p = 0.038
C: total curettage alone.
TCR+C: transcervical resection in combination with curettage.

over, the discrepancy in diagnosis between the specimen taken by TCR+C and the final diagnosis after hysterectomy was analyzed further. Regarding the pathological evaluation with TCR+C specimens among 17 patients who subsequently underwent hysterectomy, two (11.8%) were initially diagnosed as AEH by TCR+C, but the final diagnosis by hysterectomy was EC. Pathologically, the tissues taken by TCR+C had irregularly independent glands with no stromal invasion. In contrast, back-to-back glands were specifically observed with stromal disappearance in the hysterectomy specimen, which was diagnosed as EC (Figure 2). Taken together, TCR+C contributes to detecting suspected malignant lesions.

Interestingly, as shown in Table 4, various characteristic hysteroscopic imaging findings were detected in every endometrial malignant lesion. Therefore, the hysteroscopic findings were retrospectively evaluated using the current criteria focusing on the three representative aspects (atypical vessels, protruding lesions, irregular surfaces), which can often be seen in endometrial malignant lesions. In the present study, the hysteroscopic findings were classified by the criteria according to Takashima et *al.* Hysteroscopic findings showed atypical vessels in ten (73%) of the AEH cases and in 19 (75%) of the EC cases. Regarding the protruding lesions, the aspects can mostly equally be seen in both of the malignancies. Actually, the present authors consider that white desquamation may result from thickening of epithelia due to inflammation or transformation into squamous epithelium. In particular, all nine resected specimens of white desquamation with atypical vessels in the endometrium were significantly diagnosed as EC than the specimens based on other hysteroscopic findings (p = 0.0046) (Table 5). Thus, white desquamation with atypical vessels in the endometrium may be a useful finding for differential diagnosis of AEH and EC (Figure 3). However, 12 cases of EC were diagnosed even when white desquamation with atypical vessels was negative.

Discussion

The differential pathological diagnosis of endometrial malignancy, resulting from outpatient pathological diagnosis or imaging poses a therapeutic challenge due to frequent overdiagnosis, especially for patients of childbearing age or who wish to preserve ovarian function. The management and prognosis of endometrial hyperplasia and endometrial cancer are very different. Hysterectomy, with or without bilateral adnexectomy, is usually considered adequate treatment for AEH, but full surgical staging, according to current FIGO guidelines, is recommended to treat EC, even in early-stage and low-grade carcinomas, and extended pelvic surgery is advisable in the treatment of second-stage disease. Therefore, proper pre-treatment investigation for endometrial cancer is necessary for young patients who wish to preserve ovarian function. However, it has also

Table 4. — *Comparison of hysteroscopic findings and pathological diagnosis by TCR+C*

	APAM* (n=4)	AEH** (n=16)	*EC* (n=21)
Atypical vessels	**1**	**10**	**19**
Little branched vessels	0	2	1
Dilated branched vessels	1	8	18
Protruding lesions	**4**	**12**	**14**
Nodular	0	4	2
Polypoid	4	5	7
Papillary	0	3	5
Irregular surfaces	**1**	**4**	**13**
Necrosis	0	2	7
Coarse	1	2	11
Atrophic	0	0	1
White desquamation	0	4	13

TCR+C: transcervical resection in combination with curettage.
** APAM+AEH one case, APAM+EC one case included in the cases.*
*** Excludes EC two cases diagnosed after hysterectomy*
The totals do not add up because of overlapping distribution of hysteroscopic findings.

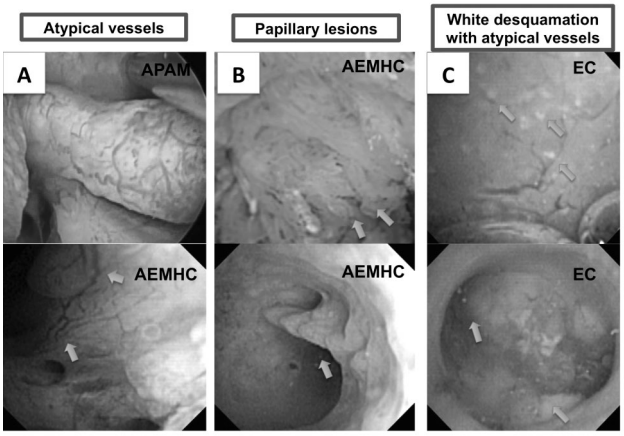

Figure 3. — Hysteroscopic imaging for endometrial malignant lesions (A) Abnormal atypical vessels are found in APAM and AEMHc. (B) Papillary protruding lesions are found in AEMHc, but without abnormal vessels in the same area. (C) White desquamation with abnormal atypical vessels is frequently observed in ECs. The cloudy background in liquid distension medium might be specific to ECs. All hysteroscopic imaging findings were diagnosed by expert hysteroscopists.

Table 5. — *Correlation between pathological diagnosis and hysteroscopic findings (n=37).*

Hysteroscopic findings	Pathological diagnosis		*p* value
	AEH	EC	
WD+AV	0	9	0.0046
AV only	10	10	0.036
WD only	3	0	0.07
none	3	2	
Total	16	21	

WD: white desquamation lesions; AV: atypical abnormal vessels; AEH: atypical endometrial hyperplasia; EC: endometrial cancer.
$p < 0.05$ considered significant.

been reported that AEH is more likely to co-exist with EC [24, 25]. Therefore, the accurate preoperative diagnosis of precancerous lesions of the endometrium is absolutely required for the optimal management of patients.

In the present study, specific hysteroscopic findings of endometrial malignancy were found using a resectoscope with a high precision angle; localized white desquamation with atypical vessels was very characteristic, and the evaluation of these various aspects in the uterine cavity may reflect a consequence of malignant transformation of the endometrial cells. In particular, white desquamation is a part of necrosis; thickening of the epithelial layers is a pattern of aberrant growth of the malignant cells, and squamous differentiation is associated with the well-differentiated glandular component. The white desquamation may result from thickening of epithelia due to inflammation or transformation into squamous epithelium. On the other hand, protruding lesions, such as nodular, polypoid, and papillary lesions, are an outcome of neoplastic growth. Extensive squamous differentiation is often present in EC, while the change can also be seen even in atypical hyperplasia diseases [26]. However, though the subject is of continued debate, the endometrial epithelium of white desquamation with atypical vessels where angiogenesis occurs may be a consequence of uniformly proliferative lesions in tumors. Thus, white desquamation with atypical vessels in the endometrium could be a useful finding for the differential diagnosis of AEH and EC.

In summary, there was less of a discrepancy between the pathological diagnosis of resected specimens by TCR+C and the final pathology than with total curettage alone, and it may be necessary to perform appropriate and precise resection of suspicious lesions with a full-angle hysteroscopic evaluation, because the management and prognosis of endometrial hyperplasia and endometrial cancer are very different. Therefore, patients should be more precisely evaluated to obtain a preoperative diagnosis of EC. Although the present study has several limitations due to small sample size, the authors consider that by using the approach of focusing the visual inspection on localized endometrial diseases, if a broad spectrum of diagnostic and operative procedures can be performed successfully, visual evaluation combined with histopathological diagnosis of resected specimens may improve preoperative staging of AEH and EC, especially for selecting treatment for the lesions. However, TCR is an invasive procedure, and its risk

and cost-benefit should be carefully considered. Furthermore, regarding the accuracy of diagnosis, even with TCR+C resected specimens, two EC cases were underdiagnosed as AEH. Thus, because of the small size and number of resected samples, there might be some difficulties in the precise diagnosis of focal lesions in the uterine cavity. Sufficient resection of the uterine muscle in focal lesions, especially for elderly patients after menopause, might help make the diagnosis. Many of the findings discussed here still require confirmation. Obviously, further investigation through accumulation of patients is warranted to verify the hysteroscopic findings that are specific for differential diagnosis using larger sample sizes.

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