Original Article

Hysterectomy through Minimally Invasive Surgery for Cervical High-grade Intraepithelial Neoplasia: Reassessment of the Specimens' Eligibility for Histological Examination

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Abstract

Objectives: The objective was to investigate the microscopic artifacts made in the uterus of cervical high-grade squamous intraepithelial lesion (HSIL) resected by hysterectomy through minimally invasive (H-MI) procedures and to verify whether these specimens are suitable for histopathological assessment.

Materials and Methods: This single-center retrospective study analyzed 28 patients with cervical HSIL, consisting of 21 premenopausal and seven postmenopausal women, who underwent H-MI. The proportion of the cervical mucosa covered by intact surface epithelium (residual ratio [RR]) was measured on microscopically. Surgical margin's status was also verified.

Results: All cases developed detachment of the cervical surface epithelium to a varying extent. The RR was significantly higher in the premenopausal patients (median: 75.5%) than in the postmenopausal patients (median: 37.6%). Among the premenopausal patients, the RR was lower in the cases on whom uterine manipulator (UM) was used (median: 70.5%) than in the cases without UM use (median 92.7%). Among the 21 cases whose resected uterus contained HSIL, the vaginal resection margin was not assessable in three (14.2%) of the seven postmenopausal cases due to the artifact.

Conclusion: Although transvaginal manipulation of the uterus causes detachment of the cervical surface epithelium, H-MI for cervical HSIL provides an acceptable specimen for histological assessment in premenopausal patients, even if UM is used. In postmenopausal women, H-MI easily develops artifactual loss of cervical surface epithelium, sometimes providing an unfavorable specimen for microscopic assessment.

Keywords: Artifact, high-grade squamous intraepithelial lesion, hysterectomy, minimally invasive surgery

Introduction

The standard management of high-grade squamous intraepithelial lesion (HSIL) of the cervix is conization or other kinds of excisional treatment such as loop electrosurgical excision procedure.[1] Hysterectomy is performed as a treatment for cervical HSIL in several clinical settings, such as patients having residual lesions after conization.[1,2] Recently, hysterectomy through minimally invasive (H-MI) procedures such as laparoscopic hysterectomy (LH) seems to be widely accepted as a surgical modality for cervical HSIL treatment in such instances.[3-7] Robot-assisted hysterectomy (RH), another type of H-MI, is another alternative.

It has been reported in the literature that hysterectomy for cervical HSIL is a risk factor of vaginal HSIL or vaginal cancer.[1,2] Although it is unclear whether the cervical HSIL

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patients after hysterectomy with positive margin have elevated risk of developing subsequent vaginal HSIL, the resection margin status of the hysterectomy specimen is usually assessed histologically to confirm whether the HSIL lesion has been completely resected. However, we have occasionally observed microscopically that the cervical superficial epithelium of the specimens resected by H-MI is partially exfoliated. Such artifacts in HSIL specimens had made histopathological assessment of the resection margin status difficult or impossible in several cases. We believe that obtaining an adequate specimen suited for the assessment of the surgical margin is preferable for optimal management after hysterectomy. If the specimens of H-MI are affected by extensive artifacts, the causes should be clarified and avoided, if possible. To our knowledge, there have been no studies in the literature investigating whether the quality of the pathological samples resected by H-MI for cervical HSIL is retained enough for microscopic assessment. For this reason, we conducted this study.

Surgeons performing H-MI for benign uterine diseases usually adopt transvaginal manipulation to make each operative procedure easier and safer. A uterine manipulator (UM), which is inserted in the uterine cavity, is commonly used because it can effectively move and stabilize the uterus during surgery.[8] We speculated that continual friction between the uterine cervix and the UM during surgery might cause detachment of the cervical superficial epithelium in H-MI. We investigated the extent of the artifactual loss of the cervical surface epithelium in the specimens resected by H-MI for cervical HSIL and examined whether the artifacts adversely affected the histopathological assessment of the surgical margin.

Materials and Methods

We conducted a retrospective review of electronic medical records to select cases with HSIL of the uterine cervix who underwent total LH or RH at our hospital between January 2018 and January 2021. As a control group without transvaginal manipulation, we randomly selected 11 premenopausal and 11 postmenopausal cases who underwent abdominal hysterectomy (AH) for indications such as ovarian tumor, uterine leiomyoma, and endometrial cancer at our hospital. All patients provided written informed consent, and the study was approved by our institutional review board (reference number: 586).

We used two types of UMs distributed by Atom Medical Corporation (Tokyo, Japan). The first type (called "UM") required a vaginal fornix delineator (VFD)[9] for colpotomy, while the second type (called "UM Total") has an attachable colpotomy cup and is similar to the Koh Colpotomizer System.[10] We used the "Vagi-Pipe," distributed by Hakko Co., Ltd. (Nagano, Japan), as our VFD.

We reexamined the hematoxylin-eosin-stained microscopic slides of the hysterectomy specimens in all cases. For each slide, we measured the length of the intact areas retaining the cervical mucosal surface epithelium, and the length of areas where the surface epithelial cells were detached or absent. We calculated the percentage of intact epithelium length within the whole cervical mucosal length and determined the mean value as the "residual ratio" of intact epithelium for each case. Vaginal resection margin was assessable if normal squamous epithelial lining was present at the vaginal side of HSIL, indicating a negative surgical margin. If the normal epithelium was completely absent on any histological slide, the margin was considered not assessable.

We used the Mann–Whitney *U*-test and the Fisher's exact test to compare differences between two groups. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[11]

Results

Clinical features

A total of 28 cases of cervical HSIL who underwent H-MI were collected; their clinical data are shown in Table 1. LH was performed in 25 cases and RH in three cases. The indications for hysterectomy included residual HSIL after conization, atrophic uterus unsuited for conization, and concomitant uterine myoma. Twenty-one women were premenopausal and the remaining seven women were

Table 1: Clinical features (*n*=28)

Features	Number of cases
Age (years old)	
41–79 (median)	47.5
Menstrual state	
Premenopausal	21
Postmenopausal	7
Type of hysterectomy	
LH	25
RH	3
Intraoperative use of UM	
Yes	21
No	7
Pathology of hysterectomy specimen	
HSIL	21
No residual lesion	7

LH: Laparoscopic hysterectomy, RH: Robot-assisted hysterectomy, UM: Uterine manipulator, HSIL: High-grade squamous intraepithelial lesion

postmenopausal. Five cases had received cone biopsy within 12 months before hysterectomy. In 23 cases, preoperative diagnosis of HSIL had been made by punch biopsy and/or endocervical curettage. The hysterectomy specimens of 21 cases revealed HSIL in the cervix. In the remaining seven cases, dysplastic epithelium was not detected in the hysterectomy specimen.

Intraoperative devices used in hysterectomy through minimally invasive surgery

We used UMs in 21 cases of H-MI. We did not use a UM in seven cases and instead inserted a VFD from the beginning of the operation. Among the 21 cases using a UM, 13 employed the "UM total" (the UM with a colpotomy cup) and eight employed the "UM" (the cup-less UM) and inserted a VFD during colpotomy.

Artifactual detachment of cervical superficial epithelium and H-MI specimens' eligibility for histological assessment of vaginal surgical margin [Tables 2 and 3].

The whole cervix was examined in all 28 cases of cervical HSIL who underwent H-MI, and the number of microscopic slides of the uterine cervix per case ranged from 4 to 10 (median: seven). In the cases of AH, most had only one microscopic slide of the cervix. On microscopic examination, each case showed varying degrees of detachment of the cervical surface epithelium. As an example, microscopic photographs of the case who underwent LH for cervical HSIL are shown in Figure 1. Thermal artifacts as shown by histological alteration in the epithelium and connective tissue were confined to the resected portion of the vagina, and most desquamated areas did not show thermal artifacts.

The data regarding the residual ratio (RR, the percentage of the area having intact surface epithelium) of the cervical surface epithelium are shown in Table 2. The RRs ranged from 9.6% to 99.4% in the cases of H-MI and from 48.0% to 100% in the cases of AH. In the both H-MI and AH groups, the RR was higher in the premenopausal women than in the postmenopausal women ($P < 0.05$). Among the premenopausal women, the RR was lower in the H-MI cohort (median: 75.5%) than the AH cohort (median: 99.0%) ($P < 0.05$). On the other hand, among the premenopausal women, there was

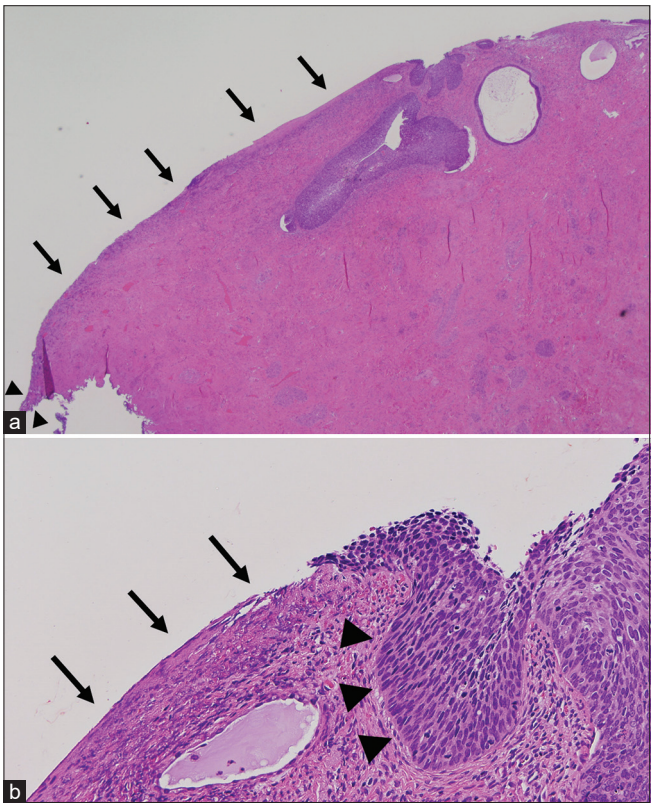

Figure 1: A postmenopausal HSIL patient who underwent laparoscopic hysterectomy (H and E), (a) x20 The surgical margin (arrowheads) was not assessable due to the loss of surface epithelium (arrows), (b) x200 Dysplastic cells involving the glands are preserved (arrowheads), but the surface is denuded (arrows). HSIL: High-grade squamous intraepithelial lesion

Table 2: Residual ratio of the cervical surface epithelium

Menstrual state	Residual ratio of the cervical surface epithelium			
	AH ($n=22$)	H-MI		
		All H-MI ($n=28$)	H-MI-UM (+) ($n=21$)	H-MI-UM (−) ($n=7$)
Premenopausal	79.6%–100%	15.0%–99.4%	15.0%–99.4%	82.6%–99.4%
	Median: 99.0%	Median: 75.5%	Median: 70.5%	Median: 92.7%
	n=11 (C-1)	n=21 (C-2)	n=17 (C-3)	n=4 (C-4)
Postmenopausal	48.0%–99.0%	9.6%–54.7%	16.8%–54.7%	9.6%–38.0%
	Median: 77.5%	Median: 37.6%	Median: 39.0%	Median: 12.1%
	n=11 (C-5)	n=7 (C-6)	n=4 (C-7)	n=3 (C-8)

This table has 8 categories/cohorts. Each category is given a number such as (C-1) in order. Comparisons between the selected two categories are as follows (Mann–Whitney *U*-test): (C-1) versus (C-2): $P<0.001$, (C-1) versus (C-4): Not significant ($P=0.601$), (C-3) versus (C-4): $P=0.001$. (C-5) versus (C-6): $P<0.001$, (C-7) versus (C-8): Not significant ($P=0.229$). (C-1) versus (C-5): $P=0.004$, (C-2) versus (C-6): $P<0.001$. H-MI-UM (+): The patients who underwent laparoscopic hysterectomy or robot-assisted hysterectomy using a UM intraoperatively, H-MI-UM (−): The patients who underwent laparoscopic hysterectomy or robot-assisted hysterectomy without a UM. AH: Abdominal hysterectomy, H-MI: Hysterectomy through minimally invasive, UM: Uterine manipulator

Table 3: Specimen's eligibility for microscopic assessment of vaginal surgical margin

	Assessable	Not assessable	*P*
Menstrual state			
Premenopausal	14	0	0.026*
Postmenopausal	4	3	
Intraoperative device			
UM (+)	15	1	0.128*
UM (−)	3	2	

*Fisher's exact test. $P<0.05$ was considered statistically significant. UM (+): The cases who underwent laparoscopic hysterectomy or robot-assisted hysterectomy using a UM intraoperatively, UM (−): The cases who underwent laparoscopic hysterectomy or robot-assisted hysterectomy without a UM. UM: Uterine manipulator

no significant difference in RR between the AH cases (median: 99.9%) and the H-MI cases without UMs (median: 92.7%), and the RR was lower in the cases using UMs (median: 70.5%) than in the cases without UMs ($P < 0.05$).

Among the 21 women whose resected uterus contained HSIL, the vaginal resection margin was not assessable in three (14.2%) of the seven postmenopausal cases due to the artifactual loss of cervical epithelial lining [Figure 1]. We used a UM for one case and did not use a UM for the other two cases. We were able to assess the resection margins in the remaining 18 cases, which were all free of dysplasia.

Discussion

First, the current study revealed that the loss of the cervical surface epithelium was more severe in postmenopausal women than in premenopausal women, not only among H-MI cases but also among AH cases. This finding suggests that postmenopausal atrophic cervical epithelium is universally vulnerable to intraoperative manipulation and other kinds of handling. In addition, it seems rational to assess the artifact seen in the cervix of hysterectomy specimens in each premenopausal and postmenopausal group separately.

Among the premenopausal women, H-MI cases with surgical UM use showed significantly worse preservation of the cervical surface epithelium than AH cases. However, preservation of the cervical surface epithelium in H-MI cases without UM use was not inferior to that of AH cases. This finding leads to the speculation that the loss of the cervical epithelium in premenopausal H-MI specimens was mainly caused by the friction of UM use. There have been two case reports dealing with histological artifact associated with H-MI for cervical HSIL.[12,13] Both of them reported cases of cervical HSIL with artifactual displacement of cervical dysplastic epithelium to fallopian tubes, which was considered to be caused by UM. Our results showing the greater epithelial loss of the cervical mucosa in premenopausal H-MI cases with UM use are consistent with these two reports, in terms of artifactual cervical epithelial displacement probably associated with UM.

Similar to premenopausal women, the H-MI specimens of postmenopausal cases also retained less cervical surface epithelium than their AH counterparts, suggesting adverse effects caused by intraoperative transvaginal devices. However, as opposed to premenopausal women, the cases with UMs and the cases without UMs both showed poor preservation of cervical surface epithelium among the postmenopausal H-MI cohort. In addition, postmenopausal H-MI specimens with UMs and those without UMs both included cases that exhibited nonassessable surgical margins. These results suggest that, among postmenopausal cases, not only UMs but other types of manipulation can also cause epithelial detachment in H-MI specimens. We speculate that VFDs might rub the cervix during the operation, but the underlying mechanisms causing epithelial loss are unclear.

Because we used electrosurgical instruments such as monopolar forceps, ultrasonic scalpels, and advanced bipolar instruments during colpotomy,[14] heat damage can be considered another possible cause of epithelial detachment. However, thermal artifacts as shown by histological alteration in the epithelium and connective tissue were confined to the resected portion of the vagina, and most desquamated areas did not show thermal artifacts in all cases. Therefore, it is unlikely that heat damage was the main cause of epithelial detachment of the cervix in both premenopausal and postmenopausal cases.

From the perspective of minimizing histopathological artifacts, H-MI performed without UMs appears to be preferable for the treatment of cervical HSIL in premenopausal women. However, we believe that H-MI with UMs can also be an option for treating premenopausal HSIL, because there was no premenopausal case in whom the vaginal resection margin of a hysterectomy specimen was not assessable histologically. Regarding postmenopausal cases, our finding suggests that simply avoiding the use of UMs would not improve the status of epithelial preservation in postmenopausal H-MI. Additional strategy for avoiding direct contact with cervical mucosa during surgery is needed.

The current study has several limitations. First, it is a retrospective study enrolling a relatively small number of cases. Second, we could not analyze all possible factors that may cause rubbing against the cervical mucosa. For example, cervical manipulation with forceps during the insertion of UMs, unintentional damage while pulling the resected uterus through the vagina, and specimen processing after surgery might have affected the cervical mucosa. In addition, we only

focused on the effects on resected specimens in this study. Although the adverse effects of surgical methods such as UM have been discussed in the literature in minimally invasive surgery for early cervical cancer,[15] the therapeutic outcome or other clinical effects given using UM or by avoiding UM in H-MI for cervical HSIL is unknown. Moreover, clinical relevance of resection margin status of hysterectomy specimen in HSIL patients remains unclear, because there have been some cases of vaginal HSIL after hysterectomy with negative surgical margin in the literature.[2,3] Therefore, our findings do not provide enough grounds for determining the optimal surgical modality for cases of cervical HSIL requiring hysterectomy.

Conclusion

Transvaginal manipulation of the uterus in H-MI causes detachment of the cervical surface epithelium to a varying extent. Despite this artifact, the specimens of H-MI for cervical HSIL are acceptable for histological assessment in the premenopausal cases even if UM is used. In postmenopausal women, H-MI easily develops artifactual loss of cervical surface epithelium, sometimes providing an unfavorable specimen for microscopic assessment.

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Conflicts of interest

There are no conflicts of interest.

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