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Importance of Colposcopy Impression in the Early Diagnosis of Posthysterectomy Vaginal Cancer

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Objective: The aim of the study was to investigate the value of cytology, high-risk human papillomavirus (hrHPV) status and colposcopy in the early diagnosis of vaginal cancer after hysterectomy.

Materials and Methods: A retrospective study was performed in the Obstetrics and Gynecology Hospital of Fudan University. Posthysterectomy patients who were diagnosed with vaginal high-grade intraepithelial lesion (HSIL) by colposcopy-directed biopsy with colposcopy impression of extensive HSIL or suspicion of cancer and underwent upper or total vaginectomy from January 2009 to December 2017 were included.

Results: Eighty-six posthysterectomy vaginal HSIL patients were included. Available abnormal cytology and positive hrHPV were observed in 90.7% (49/54) and 96.2% (51/53) of the patients, respectively. A total of 18.6% (16/86) of the patients were diagnosed with squamous cell cancer by vaginectomy, and the average interval between hysterectomy and vaginectomy was 3.5 years. Among them, 62.5% (10/16) cancers occurred after hysterectomy for cervical cancer, 31.2% (5/16) after hysterectomy for cervical precancer, and 6.3% (1/16) after hysterectomy for myoma. An indication for hysterectomy (cervical cancer vs HSIL, odds ratio = 7.2, 95% CI = 1.9–28.0, p = .004) and colposcopy impression of vaginal cancer (vaginal cancer vs HSIL, odds ratio = 5.9, 95% CI = 1.3–26.8, p = .021) were high-risk factors of cancer confirmed by vaginectomy in colposcopy-directed biopsy vaginal intraepithelial neoplasia 2/3 posthysterectomy in multiple logistic regression analysis.

Conclusions: Colposcopy is pivotal in the evaluation of abnormal cytology/hrHPV tests in follow-up of cervical cancer patients after hysterectomy and decision-making for vaginectomy in detecting early cancer.

Key Words: colposcopy, vaginectomy, cancer

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The current consensuses and guidelines for cervical cancer screening are adequate and regularly updated.[1–4] The current cervical cancer screening guidelines recommend that high-risk groups, such as women who have had cervical precancer (high-grade squamous intraepithelial lesions [HSIL]) or invasive cervical cancer, undergo continued surveillance testing for at least 20 years after treatment.[4] Because of the rarity of vaginal cancer, there are currently no formal guidelines recommending screening for vaginal cancer in the general population.[5] Many such women have cytology and/or co-testing (cytology and hrHPV testing) performed.[4,6] This leaves clinicians with the dilemma of how to manage these abnormal vaginal screening tests.[5] In addition, the available literature is significantly limited in terms of the development of evidence-based recommendations in managing abnormal vaginal cytology and high-risk human papillomavirus (hrHPV) screening tests after hysterectomy.

In the largest women's hospital of China, the Obstetrics and Gynecology Hospital of Fudan University (OGHFU), women, including those who are posthysterectomy or not, undergo regular cytology and/or hrHPV testing; those with abnormal screening reports are referred to colposcopy and vaginal intraepithelial neoplasia (VaIN) was diagnosed with colposcopy-directed biopsy. The detection rate of total VaIN (VaIN 1 and VaIN 2/3) in all lower genital tract intraepithelial lesions was 11% (1,923/16,732, VaIN 1: 9% [1,561/16,732], VaIN 2/3: 2% [362/16,732]) on average with an increasing trend from 2013 to 2015 in our hospital.[7] Generally, vaginal HSIL patients diagnosed with colposcopy-directed biopsy can be effectively treated with ablation and medication. In our hospital, carbon dioxide laser is routinely used to treat VaIN 2/3.

Under 2 circumstances, vaginectomy can be performed in posthysterectomy VaIN 2/3 patients to exclude cancer. First, colposcopy impression was suspicion of cancer. Second, extensive HSIL was present in upper vagina, including vaginal dimples where sufficient inspection and biopsy are hard to achieve. However, the value of cytology, hrHPV status, colposcopy, and vaginectomy in the diagnosis of vaginal cancer after hysterectomy remains unclear. Here, a retrospective study of vaginectomy was performed to systematically investigate their values in the early diagnosis of vaginal cancer after hysterectomy.

MATERIALS AND METHODS

A retrospective computer-based search was performed. Subjects were enrolled from January 2009 to December 2017 in OGHFU. In OGHFU from January 2009 to December 2017, a total of 26,689 patients underwent loop electrosurgical excision procedure (LEEP) for cervical HSIL, and 5,889 HSIL patients underwent hysterectomy for atrophic cervix in which LEEP cannot be performed or for positive margins after LEEP. For cervical cancer, a total of 1,266 patients underwent hysterectomy for IA1; 7,442 patients underwent modified or radical hysterectomy for IA2-IIA1. Inclusion criteria included posthysterectomy patients who were diagnosed with vaginal HSIL by colposcopy-directed biopsy with colposcopy impression of extensive HSIL or suspicion of cancer and underwent upper or total vaginectomy, and the use of radiation as initial treatment or adjuvant treatment did not affect inclusion. Exclusion criteria included posthysterectomy patients diagnosed with vaginal cancer by colposcopy-directed biopsy. A flow chart of the study design was illustrated in Figure 1. Approval was obtained from institutional review board of the OGHFU before data extraction was performed. The requirement for written informed consent was waived by the institutional review board. Informed consent to participate in the research was obtained by telephone interview.

The colposcopy features of HSIL include dense acetowhite epithelium, coarse mosaic, coarse punctuation, rapid appearance of acetowhitening, cuffed crypt (gland) openings, sharp border, inner border sign, and ridge sign. The colposcopy features of

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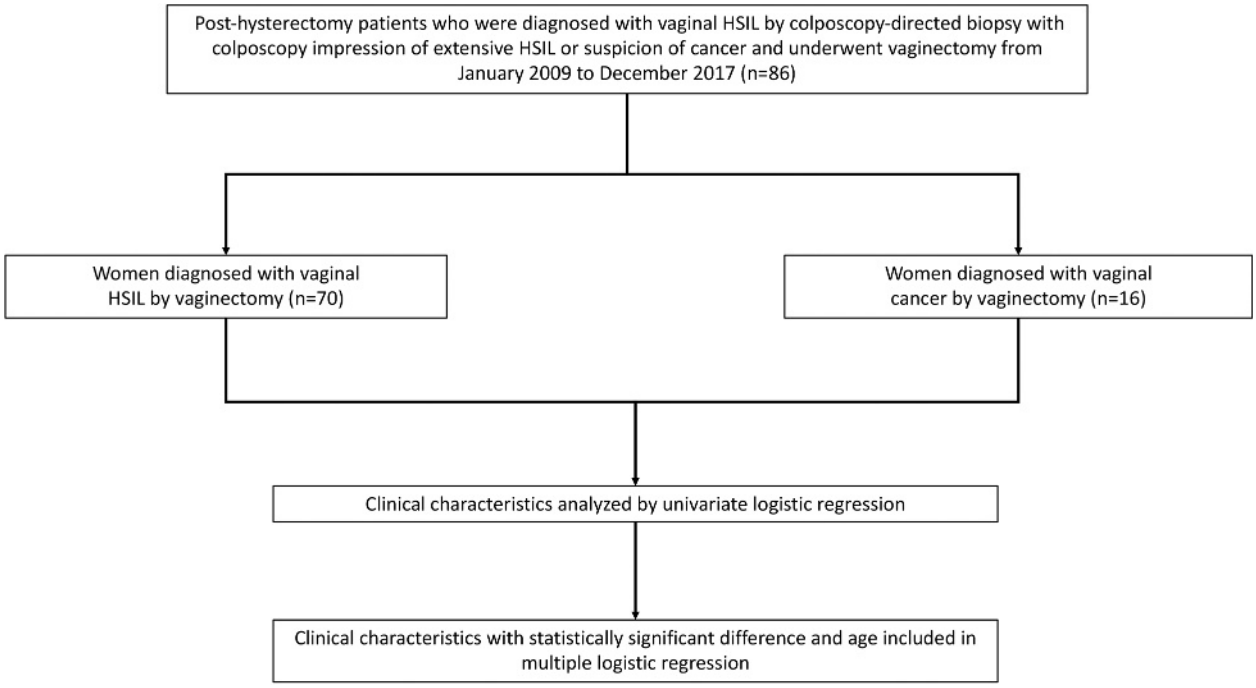

FIGURE 1. A flow chart of the study design.

suspicion of cancer include atypical vessels, fragile vessels, irregular surface, exophytic lesion, necrosis, ulceration, tumor, or gross neoplasm.[8] Dense acetowhite epithelium can exist in early stages and disappear as cancer progresses.

All pathologic specimens were processed by a standardized protocol, interpreted by an experienced staff pathologist, and then verified by another advanced pathologist. Abdominal (including open and laparoscopic) and vaginal vaginectomy was performed to exclude cancer. Cystoscopy and bilateral ureteral stents were placed intraoperatively in a portion of the included patients.

The study subjects were divided into 2 groups (vaginal HSIL vs vaginal cancer) to investigate associated high-risk factors of vaginal cancer according to the results of vaginectomy. Baseline clinical characteristics of the study subjects were analyzed by univariate logistic regression in Table 1. Quantitative data were expressed as mean ± SD. Statistical significance was defined as $p < .05$. Variables with statistically significant difference in Table 1 were included in a multiple logistic regression in Table 2 and $p < .05$ was defined statistically significant. Statistical analyses were performed using SPSS 20 (IBM SPSS statistics, Armonk, NY).

RESULTS

Clinical Characteristics of the Patients Who Underwent Vaginectomy

A total of 86 posthysterectomy patients diagnosed with vaginal HSIL by colposcopy-directed biopsy with colposcopy impression of extensive HSIL or suspicion of cancer underwent vaginectomy in our hospital. Among them, 94.2% (81/86) of women hysterectomized in other units were referred to our colposcopy department for abnormal cytology and/or hrHPV results. The other 5.8% (5/86) of women underwent hysterectomy in our hospital. According to the results of vaginectomy, the study subjects were divided into 2 groups (vaginal cancer vs vaginal HSIL) to investigate associated high-risk factors of vaginal cancer. Baseline clinical characteristics of the study subjects were analyzed by univariate logistic regression in Table 1. Their mean ± SD age was 54 ± 9 years (range = 37–79 years). The mean ± SD time interval between hysterectomy and vaginectomy was 3.5 ± 3.5 years (range = 0.25–22 years). The 51-year-old patient with the minimal interval underwent radical hysterectomy for cervical cancer IB1 and was referred to colposcopy after 3 months with cytology of negative for intraepithelial lesion or malignancy and positive hrHPV testing. Vaginal HSILs were diagnosed with colposcopy-directed biopsy and then confirmed by vaginectomy. The 63-year-old patient with the maximal interval underwent hysterectomy for myoma in 1996 when she was 41 years old and was referred to colposcopy for vaginal cytology of HSIL and positive hrHPV testing after 22 years. Vaginal HSIL was then diagnosed with colposcopy-directed biopsy and also confirmed by vaginectomy.

The indication of hysterectomy included 3 myoma, 1 abnormal uterine bleeding (ovulatory disorder), 56 cervical HSIL, and 26 cervical cancers. Of the 3 patients who underwent hysterectomy for myoma, 1 with a cytology of HSIL and positive hrHPV testing was confirmed as having cancer, and the other 2 with cytology of HSIL and atypical squamous cells-cannot exclude HSIL and positive hrHPV results were confirmed as having vaginal HSIL. In addition, 1 patient who underwent hysterectomy for postmenopausal ovulatory disorder has a low-grade vaginal intraepithelial lesion (LSIL) cytology result. Their intervals between hysterectomy and vaginectomy are 15, 19, 22, and 6 years, respectively, with a mean interval of 15.5 years. All 26 cervical cancer patients underwent initial treatment of hysterectomy, modified or radical hysterectomy according to their stages, including 11 IA1, 3 IA2, 9 IB1, 1 IB2, and 2 IIA1. According to surgical findings, 4 of 9 IB1, 1 of 1 IB2, and 1 of 2 IIA1 patients underwent adjuvant treatment of radiation and concurrent chemotherapy. However, 1 IB1 and 1 IIA1 patients declined adjuvant treatment above for personal reasons.

Available abnormal cytology and positive hrHPV were observed in 90.7% (49/54) and 96.2% (51/53) of the patients, respectively. Forty-three posthysterectomy vaginal HSIL patients diagnosed with colposcopy-directed biopsy had co-testing results

TABLE 1. Clinical Characteristics of Posthysterectomy Vaginal HSIL Patients Diagnosed With Colposcopy-Directed Biopsy Who Underwent Vaginectomy to Exclude Cancer

Characteristics	Total no. undergoing vaginectomy (n = 86)	Histology from vaginectomy		% of cancer (18.6%)	p (<.05*)
		HSIL (n = 70)	Cancer (n = 16)		
Age, mean ± SD, y	54 ± 9	54 ± 8	52 ± 11		.407
30–39	8	4	4	50.0%	
40–49	16	14	2	12.5%	
50–59	41	34	7	17.1%	
>60	21	18	3	14.3%	
Time interval between hysterectomy and vaginectomy, y	3.5 ± 3.5	3.1 ± 3.5	3.5 ± 3.5		.705
Indication for hysterectomy[a]					.004*
Myoma/AUB	4	3	1	25.0%	
HSIL	56	51	5	8.9%	
Cancer	26	16	10	38.5%	
IA1	11	7	4	36.4%	
IA2	3	2	1	33.3%	
IB1	9	5	4	44.4%	
IB2	1	1	0	0.0%	
IIA1	2	1	1	50.0%	
Vaginal cytology (n = 54)					.391
<HSIL[b]	20	17	3	15.0%	
HSIL+[c]	34	31	3	8.8%	
Vaginal hrHPV (n = 53)					.751
Positive	51	44	7	13.7%	
Negative	2	2	0	0.0%	
Colposcopy impression					.006*
Extensive HSIL	43	40	3	7.0%	
Suspicious of SCC	43	30	13	30.2%	
Colposcopy-directed biopsy					.036*
HSIL	78	66	12	15.4%	
HSIL suspicious of SCC	8	4	4	50.0%	

*Statistically significant $p < .05$.

[a]The p value .004 is the comparison between cervical HSIL and cancer as the indications of hysterectomy.

[b]<HSIL includes negative for intraepithelial lesion or malignancy, atypical squamous cells of undetermined significance, and LSIL.

[c]HSIL+ includes atypical squamous cells-cannot exclude HSIL, HSIL, and SCC.

AUB indicates abnormal uterine bleeding.

of cytology and hrHPV. Among them, 83.7% (36/43) had abnormal cytology results (including atypical squamous cells of undetermined significance, atypical squamous cells-cannot exclude HSIL, LSIL, HSIL, and squamous cell carcinoma [SCC]) and positive hrHPV simultaneously; 11.6% (5/43) had normal cytology results and positive hrHPV; 4.7% (2/43) had negative hrHPV and abnormal cytology; and none had double negative co-testing results (Supplementary Table 2, http://links.lww.com/LGT/A101).

A total of 18.6% (16/86) of the patients were diagnosed with squamous cell cancer on final pathologic examination by vaginectomy. Among them, 62.5% (10/16) cancers occurred after hysterectomy for cervical cancer, 31.2% (5/16) after hysterectomy for cervical precancer, and 6.3% (1/16) after hysterectomy for myoma. (Supplementary Table 1, http://links.lww.com/LGT/A101), with cancer significantly more than precancer as indication for hysterectomy (cervical cancer vs HSIL = 38.5% vs 8.9%, p = .004). Cancer was diagnosed significantly more in vaginal HSIL cases with a colposcopy impression of suspicion of cancer than those with extensive HSIL (vaginal cancer vs HSIL = 30.2% vs 7.0%, p = .006). Cancers were significantly more detected in colposcopy-directed biopsy results of HSIL suspicious of cancer than HSIL (vaginal cancer vs HSIL = 50.0% vs 15.4%, p = .036). Baseline clinical characteristics with statistically significant difference, including indication for hysterectomy, colposcopy impression, and colposcopy-directed biopsy in Table 1, were included and adjusted by age in a multiple logistic regression. An indication for

TABLE 2. Multiple Logistic Regression Analysis of High-Risk Factors of Cancer Based on Univariate Logistic Regression Analysis of Baseline Clinical Characteristics

High-risk factors	OR	95% CI	p (<.05*)
Indication for hysterectomy	7.2	1.9–28.0	.004*
Colposcopy impression	5.9	1.3–26.8	.021*
Colposcopy-directed biopsy	4.1	0.7–24.7	.127
Age	1.0	0.9–1.1	.632

*Statistically significant $p < .05$.

Baseline clinical characteristics with statistically significant difference in Table 1 were included and adjusted by age in multiple logistic regression.

hysterectomy (cervical cancer vs HSIL, odds ratio [OR] = 7.2, 95% CI = 1.9–28.0, $p = .004$) and colposcopy impression of vaginal cancer (vaginal cancer vs HSIL, OR = 5.9, 95% CI = 1.3–.26.8, $p = .021$) were demonstrated to be high-risk factors of vaginal cancer with statistically significant difference (see Table 2). In addition, 37.5% (3/8) of vaginal excrescences diagnosed with HSIL by punch biopsy with diameters ranging from 8 to 20 mm were confirmed as cancer, and the rest 5 excrescences were diagnosed with 3 HSIL, 1 LSIL, and 1 chronic inflammation. Thirty-one of 43 of extensive HSIL had vaginal dimples where sufficient inspection and biopsy is hard to achieve. The reasons for the insufficient inspection of the vagina included adhesion after laser ablation (67.7%, 21/31) and suture of the 2 ends of the vaginal apex to the cardinal ligament stump in hysterectomy (32.3%, 10/31). After vaginectomy, 12 (75.0%) of 16 carcinomas confined to the vaginal wall were diagnosed as International Federation of Gynecology and Obstetrics stage I carcinomas, and 4 (25.0%) of 16 carcinomas extending beyond the vagina into the paravaginal tissues were diagnosed as International Federation of Gynecology and Obstetrics stage 2 carcinomas; radiation therapy was performed thereon.

Follow-Up

The median follow-up period of 4.5 years (range = 0.3–9.2 years). In the 16 patients with vaginal cancer who underwent radiotherapy and chemotherapy, 5 had normal cytology, hrHPV, and pelvic magnetic resonance imaging reports; 3 patients who underwent total vaginectomy had normal pelvic magnetic resonance imaging reports; 1 patient had biopsy-confirmed vaginal LSIL; 2 patients survived but failed to come back to hospitals; and 5 patients changed their telephone numbers and were lost to follow-up.

The estimated cure rate for vaginal HSIL patients by vaginectomy is between 62.9% (44/70) and 95.6% (44/46). Of the 70 vaginal HSIL patients, 1 was diagnosed with cancer recurrence in the pelvic cavity 11 months after vaginal vaginectomy. The patient had undergone radical hysterectomy 12 months before vaginectomy for stage IB2 cervical squamous carcinoma. After pelvic recurrence, the patient underwent radiotherapy and survived. One patient had recurrence of vaginal HSIL and planned to undergo total vaginectomy. In 44 patients with cytology, hrHPV, and colposcopy reports, 72.7% (32/44) had normal cytology, hrHPV, and colposcopy report s and 27.3% (12/44) were had normal cytology and colposcopy but hrHPV positive reports. Ten patients returned to local hospitals and only reported good general situation. Fourteen patients were lost to follow-up.

DISCUSSION

In 2012, as part of the lower anogenital squamous terminology standardization project for hrHPV-associated lesions, the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology proposed revised terminology by which VaIN can be reported using a 2-tiered nomenclature: LSILs for low-grade disease (VaIN 1) and HSIL for high-grade disease (VaIN 2/3).[9] In the treatment of vaginal HSIL, carbon dioxide laser vaporization is a common choice, with a cumulative cure rate of 69% (53/77) to 96% (273/285).[10–15] Chemical treatment (5-fluorouracil) cream was curative in 46% (5/11) to 100% (17/17, most patients had undergone radiation for malignancy) of VaIN cases.[15–17] Recently, Rhodes et al.[18] reported that intravaginal estrogen therapy for vaginal HSIL (VaIN 2/3) was an alternative to standard therapies with a success rate of 90% (36/40). However, the previously stated treatment failed in some patients and was unsuitable for those with a vaginal HSIL pathology but suspected cancer by colposcopy impression. In addition, the vaginal apex after hysterectomy is thin and often difficult to expose; hence, punch biopsy can be insufficient. Under such circumstances, vaginectomy could be performed to further detect and treat potential cancers; cancers were reported in 4.6% to 28% of patients with vaginal HSIL (VaIN 2/3).[19–21] The disadvantages of vaginectomy include risks of hemorrhage, injury to the bladder or rectum, and vaginal shortening or stenosis.[20,22,23]

In a study of patients with invasive cervical cancer who were treated with hysterectomy and follow-up for an average period of 3.5 years, VaIN was detected in 54.5% (6/11) of patients with a positive hrHPV result and 16.7% (6/36) of those with a negative hrHPV result.[24] In our study, abnormal cytology and positive hrHPV were observed in 90.7% (49/54) and 96.2% (51/53) of the patients. In addition, hrHPV infection may co-exist and persist in patients undergoing hysterectomy for benign diseases. Persistent hrHPV infection may cause vaginal HSIL and cancer. Hence, cytology and hrHPV results might be suitable for posthysterectomy patients especially those with a cervical precancer/cancer history and can be used to refer patients with potential vaginal lesions to colposcopy. It is only through colposcopy that patients can be further examined and the severity of vaginal lesions evaluated.

In our study, 18.6% (16/86) of vaginal HSIL patients after hysterectomy were diagnosed with cancer by vaginectomy. In the literature review, 4.6% (4/86) and 12% (13/105) of VaIN 2/3, and 28% (9/32) of VaIN 3 patients were diagnosed with cancer by excisional procedures after hysterectomy, respectively.[19–21] We previously reported that the sensitivity of cytology and hrHPV for biopsy-proven VaIN is noninferior to the sensitivity of cytology and hrHPV for biopsy-proven cervical intraepithelial neoplasia (CIN) 2+ and can help early detection of VaIN. The sensitivity of cytology for VaIN 2/3 after hysterectomy was 80.8% (21/26) and 58.8% (20/34) in patients without hysterectomy. The sensitivity of hrHPV for VaIN 2/3 after hysterectomy was 92.3% (24/26) and 93.5% (29/31) in patients without hysterectomy. The sensitivity of co-testing for VaIN 2/3 after hysterectomy was 100%

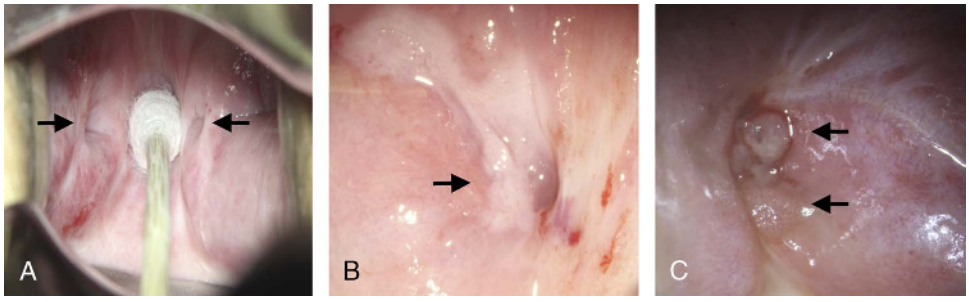

FIGURE 2. Colposcopy examination of the vaginal apex after hysterectomy. A, Vaginal dimples, which are difficult to inspect and biopsy. B, High-grade intraepithelial lesion extending into vaginal dimples. C, Suspicion of cancer in the colposcopy impression, HSIL in the colposcopy-directed biopsy, and cancer by vaginectomy.

(22/22) and 92.0% (23/25) in patients without hysterectomy.[25] In this study, cytology, hrHPV, and co-testing sensitivity for posthysterectomy vaginal HSIL+ (including vaginal HSIL and cancer confirmed by vaginectomy) is 90.7% (49/54), 96.2% (51/53), and 100% (43/43). Both studies demonstrated high sensitivities of vaginal cytology, hrHPV, and co-testing in detection of posthysterectomy vaginal HSIL+.

Colposcopy is essential for the early detection of vaginal cancer. When the pathology of colposcopy-directed biopsy showed vaginal HSIL whereas the colposcopy impression is suspicion of cancer, up to 30.2% of cases were confirmed as having cancer by vaginectomy in our study. For the early detection of VaIN or invasive cancers, suturing the vagina transvaginally help sufficiently inspect vaginal epithelia through colposcopy. In the laparoscopic and abdominal suturing of the vagina, the 2 ends of the vaginal apex should not be sutured to the cardinal ligaments stump to avoid the formation of vaginal dimples that are difficult to inspect and biopsy in colposcopy (see Figure 2).

CONCLUSIONS

Colposcopy is pivotal in not only the evaluation of abnormal cytology/hrHPV tests after hysterectomy but also decision-making for vaginectomy in the detection of early cancer.

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