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*Original Article*

# Abnormal Vaginal Cytology after Total Laparoscopic Hysterectomy in Patients with Cervical Intraepithelial Neoplasia

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**To explore the incidence of abnormal vaginal cytology after total laparoscopic hysterectomy for the treatment of cervical intraepithelial neoplasia 3, we retrospectively analyzed the medical records of patients treated at NHO Shikoku Cancer Center (Japan) in 2014-2019. The cases of 99 patients who underwent a laparoscopic (n = 36) or open (n = 63) hysterectomy and postoperative follow-up were examined. Abnormal vaginal cytology was detected in 13.9% (5/36) of the laparoscopic-surgery (LS) group and 14.3% (9/63) of the open-surgery (OS) group. A vaginal biopsy was performed at the physicians' discretion; one LS patient and six OS patients were diagnosed with vaginal intraepithelial neoplasia. The cumulative incidence of abnormal vaginal cytology at 3 years post-hysterectomy was 21.4% (LS group) and 20.5% (OS group), a nonsignificant difference. A multivariate analysis showed that age > 50 years was the only independent risk factor for abnormal vaginal cytology among the covariates examined including age; body mass index; histories of vaginal delivery, abdominal surgery, and smoking; and surgical approach (hazard ratio 8.11; 95% confidence interval 1.73-37.98; $p = 0.01$). These results suggest that the occurrence of abnormal vaginal cytology after a hysterectomy may not be influenced by the laparoscopic procedure but is associated with older age.**

**Key words:** total laparoscopic hysterectomy, vaginal intraepithelial neoplasia, cervical intraepithelial neoplasia, vaginal cytology, risk factor

Women with a history of uterine cervical intraepithelial neoplasia (CIN) or cervical cancer have a higher risk of vaginal intraepithelial neoplasia (VAIN) compared to those without such a history [1]. Several studies have reported that (*i*) VAIN occurs in 1-10% of patients who undergo a total hysterectomy for CIN, and (*ii*) the risk of vaginal cancer increases over a 20-year period in these patients [2,3]. Recent guidelines recommend that surveillance for VAIN should be continued for women with a history of high-grade CIN (CIN2 or 3) for at least 20 years after the completion of CIN treatment [4]. The most common presentation of VAIN is abnormal cytology without clinical symptoms, and vaginal cytology is generally performed for surveillance [2,5].

The standard treatment for CIN3 is cervical conization. A total hysterectomy without conization is an option as the initial surgery for women who do not wish to preserve their uterus or who are elderly and in whom invasive cancer is ruled out by a careful evaluation of cervical lesions [6]. Compared to the conventional open hysterectomy, a total laparoscopic hysterectomy offers a shorter hospital stay, quicker resumption of postoperative activity, and cosmetic advantages [7]. Total laparoscopic hysterectomy has become a treat-

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ment option for CIN3 in Japan, and it is the procedure of choice for patients with early-stage cervical cancer at institutions that meet the criteria [7,8] (https://www.jsog.or.jp/modules/committee/index.php?content_id=161, accessed May, 2023).

However, the incidence of VAIN after a total laparoscopic hysterectomy is less clear compared to that after a conventional open hysterectomy. We conducted the present study to explore the incidence of abnormal vaginal cytology in patients who have undergone a total laparoscopic hysterectomy for the treatment of CIN3 and to determine the factors associated with the occurrence of abnormal vaginal cytology.

## Patients and Methods

This retrospective cohort study was conducted using the medical records of patients who underwent a total hysterectomy for CIN3 treatment during the 6-year period from January 2014 to December 2019 at the NHO Shikoku Cancer Center (Matsuyama, Japan). Patients postoperatively diagnosed with concurrent invasive cancer or cervical glandular abnormalities were excluded. At the NHO Shikoku Cancer Center, the postoperative surveillance after a hysterectomy for the treatment of CIN3 includes gynecological examinations and vaginal cytology. This surveillance is usually initiated 4-6 months after the hysterectomy and is repeated at 6- to 12-month intervals, with specimens collected from the vaginal vault for liquid-based cytology testing.

The study data were collected as of December 2022 and included clinical characteristics, surgical procedure, operating time, estimated blood loss, perioperative complications, histological diagnosis of the removed uterus, the postoperative follow-up period, postoperative vaginal cytology results, and histological findings in cases in which a vaginal colposcopy-directed biopsy was performed. Perioperative complications were defined as any event deviating from a normal postoperative course within 30 days after surgery, according to the Clavien-Dindo classification [9]. The resection margin on the vaginal side of the removed uterus was considered positive when high-grade CIN was observed. The postoperative follow-up period was defined in this study as the time from the patient's hysterectomy to her last vaginal cytology examination. Abnormal vaginal cytology was defined as the presence of a presumed low-grade or higher squamous intraepithelial lesion (SIL) in the vagina.

At the NHO Shikoku Cancer Center, human papillomavirus (HPV) testing is not offered as a clinical examination for all patients diagnosed with CIN3, but patients are offered the opportunity to participate in clinical trials. Patients who participate in a clinical trial can be evaluated for HPV infection prior to the initiation of treatment.

Fisher's exact test was used for the statistical analysis of categorical variables, and the Mann–Whitney *U*-test was used for continuous variables. We calculated the incidence rates per person-years and the cumulative incidence of postoperative abnormal vaginal cytology stratified by the surgical approach. The log-rank test and Cox proportional hazards regression model were used to compare the incidences of abnormal postoperative vaginal cytology. All *p*-values were two-sided, and $p$-values $< 0.05$ were considered 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) [10].

This study was approved by the Institutional Ethics Review Committee of the NHO Shikoku Cancer Center (approval no. 2021-73) and was performed in accord with the Ethical Guidelines for Medical and Health Research involving Human Subjects.

## Results

During the above-described study period, 106 patients underwent a total hysterectomy for CIN3 treatment at the NHO Shikoku Cancer Center, and 99 of the 106 patients who underwent postoperative follow-up were included in this study. All patients underwent a colposcopic examination before the hysterectomy by a gynecologic oncologist for the assessment of the resectability of cervical lesions, and the 99 patients underwent an extrafascial simple total hysterectomy via the laparoscopic approach (36 patients [36.4%], laparoscopic surgery group) or open approach (63 patients [63.6%], open surgery group). The Shikoku Cancer Center started providing total laparoscopic hysterectomy as a treatment for CIN3 in 2016. A conventional open hysterectomy was performed for patients with a history of laparotomy, no history of vaginal delivery, or an estimated uterine weight of $\geq 500$ g, at the discretion

of their physicians.

In all 36 patients in the laparoscopic surgery group, a total laparoscopic hysterectomy was performed under the standard procedure [11] with the patient in a moderate Trendelenburg position (10°-15°) with carbon dioxide pneumoperitoneum (8-12 mmHg), and four trocars were placed according to the diamond principle: a 12-mm trocar at the umbilicus to accommodate the laparoscope, and one 12-mm and two 5-mm trocars in the left, middle, and right lower abdomen (Fig. 1). For patients in whom a uterine manipulator could be inserted into the uterine cavity, the manipulator was used for appropriate uterine mobilization. For patients in whom a uterine manipulator could not be inserted into the uterine cavity, a vaginal pipe was used instead of a uterine manipulator.

Bilateral uterine arteries and ureters were exposed to the greatest extent possible. Single-stitch suturing was performed at the site where the uterine artery entered the parametrium as a landmark to avoid ureteral injury during hemostatic manipulation and vaginal wall suturing. The vaginal incision was made using a monopolar electrocautery unit along the upper edge of the cup of the uterine manipulator or the vaginal pipe. The vaginal wall was sutured intraperitoneally. None of the patients who underwent a laparoscopic surgery were converted to open surgery. In all patients in the open surgery group, a transabdominal hysterectomy was also performed according to the standard procedure [8], and the vaginal incision was made using a monopolar electrocautery unit. All surgeries were performed by certified gynecological oncologists as primary or assistant surgeons.

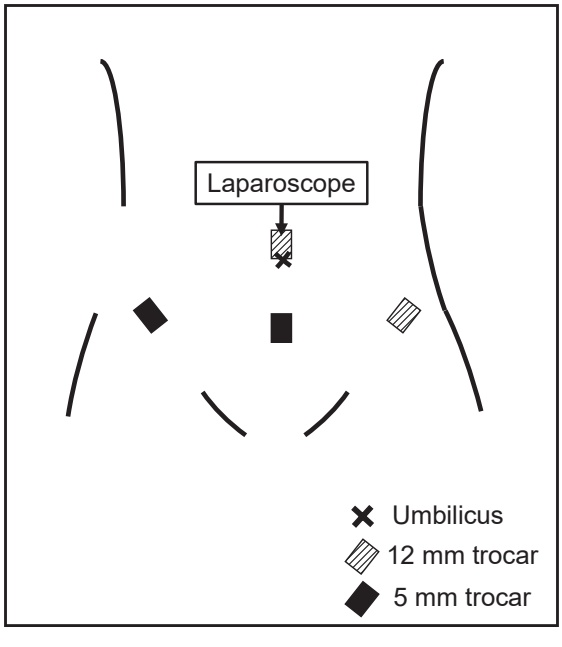


**Fig. 1** Trocar insertion sites in the patients' total laparoscopic hysterectomies (TLHs). Each TLH was performed using the standard procedure, and four trocars were placed according to the diamond principle: a 12-mm trocar at the umbilicus to accommodate the laparoscope and one 12-mm and two 5-mm trocars in the left, middle, and right lower abdomen, respectively.

Table 1 summarizes the clinical characteristics of the 99 patients. The median age and body mass index (BMI) at hysterectomy and the proportions of patients with a history of vaginal delivery or smoking were not significantly different between the laparoscopic and open surgery groups. A history of abdominal surgery was significantly more common in the open surgery group than in the laparoscopic surgery group (39.7% vs. 19.4%, $p = 0.04$).

Eleven patients had a history of cervical conization before hysterectomy, and the proportion of these patients was significantly higher in the laparoscopic surgery group compared to the open surgery group (22.2% vs. 4.8%, $p = 0.02$). Of the 99 patients, only eight (8.0%) had been tested for HPV infection, and the test was performed in another clinical trial. No patient in either group had a history of immunodeficiency or disease that would be an indication for immunosuppressive drugs.

The median operation time was significantly longer in the laparoscopic surgery group versus the open surgery group (165 vs. 130 min, $p < 0.001$). The estimated blood loss was not significantly different between the groups. The weight of the removed uterus was not recorded in about half of the patients in each group, and a between-group comparison of these values was not conducted. The median length of hospital stay was significantly longer in the open surgery group (14 vs. 9.5 days, $p < 0.001$).

Perioperative complications occurred in six of the 99 patients (6.0%): pelvic abscess (grade II, two patients) in the laparoscopic surgery group, and retroperitoneal abscess (grade II, one patient), ischemic heart disease (grade II, one patient), and pelvic abscess (grade II, two patients) in the open surgery group. The postoperative pathological diagnoses revealed a positive vaginal margin of the removed uterus in only one patient in the

Table 1 The characteristics of the patients (n = 99) who underwent a total laparoscopic hysterectomy by the open or laparoscopic approach for cervical intraepithelial neoplasia (CIN)3

| | | Laparoscopic surgery group (n = 36) n (%) | Open surgery group (n = 63) n (%) | *P*-value |
|---|---|---|---|---|
| Age at time of hysterectomy (year) | median [range] | 49 [38–77] | 51 [24–77] | 0.93 |
| BMI (kg/m$^2$) | median [range] | 22 [18–30] | 22 [16–35] | 0.67 |
| History of vaginal delivery | yes | 27 (75.0) | 53 (84.1) | 0.51 |
| | no | 5 (13.9) | 6 (9.5) | |
| | NA | 4 (11.1) | 4 (6.3) | |
| History of smoking | yes | 17 (47.2) | 39 (61.9) | 0.39 |
| | no | 17 (47.2) | 23 (36.5) | |
| | NA | 2 (5.6) | 1 (1.6) | |
| History of abdominal surgery | yes | 7 (19.4) | 25 (39.7) | 0.04 |
| | no | 27 (75.0) | 34 (54.0) | |
| | NA | 2 (5.6) | 4 (6.3) | |
| History of conization for CIN treatment | yes | 8 (22.2) | 3 (4.8) | 0.02 |
| | no | 28 (77.8) | 60 (95.2) | – |
| HPV infection | tested in another clinical trial | 2 (5.6) | 6 (9.5) | – |
| | not tested | 34 (94.4) | 57 (90.5) | – |
| Operating time (min) | median [range] | 165 [91–265] | 130 [92–291] | < 0.001 |
| Estimated blood loss (ml) | median [range] | 67.5 [0–550] | 80 [5–565] | 0.50 |
| Length of hospital stay (day) | median [range] | 9.5 [7–14] | 14 [8–22] | < 0.001 |
| Perioperative complications | yes | 2 (5.6) | 4 (6.3) | 1.00 |
| | no | 34 (94.4) | 59 (93.7) | |
| Positive vaginal margin | n (%) | 0 | 1 (1.6) | NA |

BMI, body mass index; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; NA, not available.

open surgery group.

Postoperatively, all patients underwent gynecological examinations and vaginal cytology. All cytological specimens were obtained from the vaginal vault and subjected to liquid-based tests. Postoperative vaginal cytology was initiated 4-6 months after the hysterectomy and repeated at 6- to 12-month intervals. Table 2 summarizes the patient management after the hysterectomy. The median postoperative follow-up was 27 months for both groups, and the number of vaginal cytology examinations per patient was $3.7 \pm 1.4$ and $4.0 \pm 2.9$ (mean $\pm$ SD) in the laparoscopic and open surgery groups, respectively, with no significant difference. Abnormal vaginal cytology was detected in five patients in the laparoscopic surgery group (5/36, 13.9%) and nine in the open surgery group (9/63, 14.3%). Abnormal cytology was first detected 19 and 12 months post-hysterectomy in the laparoscopic and open surgery groups, respectively. One patient in the open surgery group, in which the vaginal margin of the removed uterus was positive, showed no abnormal cytology during her follow-up.

All abnormal vaginal cytology results in the laparoscopic surgery group were identified to be low-grade SIL (5/36 patients, 13.9%). In the open surgery group, low-grade SIL was identified in three patients (4.8%), and high-grade SIL was identified in six patients (9.5%). Vaginal colposcopy-directed biopsies were performed at the physicians' discretion in both groups; one laparoscopic-group patient and six open-group patients were diagnosed with VAIN. Among these seven patients, low-grade VAIN was confirmed in four patients and high-grade VAIN was confirmed in three patients. Two of the patients with high-grade VAIN underwent laser vaporization, and the remaining five patients underwent observational follow-up. No patients were diagnosed with vaginal cancer during the postoperative follow-up.

Figure 2 depicts the cumulative incidence of abnormal vaginal cytology according to the surgical approach. The cumulative incidence rate at 3 years post-hysterectomy was 21.4% in the laparoscopic group and 20.5% in the open group ($p=0.96$). The cumulative incidence did not increase beyond 3 years of postoperative follow-up in either group.

The results of the multivariate analysis demonstrated that age >50 years was significantly associated with postoperative abnormal vaginal cytology among the covariates including age, BMI, history of vaginal delivery, history of abdominal surgery, history of smoking, and surgical approach (hazard ratio 8.11; 95% confidence interval 1.73-37.98; $p=0.01$) (Table 3).

## Discussion

Our analyses revealed that 13.9% (5/36) of patients who underwent a total laparoscopic hysterectomy for CIN3 developed abnormal vaginal cytology. The cumu-

**Table 2** Summary of the patients' post-hysterectomy management

| | | Laparoscopic surgery group (n=36) | Open surgery group (n=63) | *P*-value |
|---|---|---|---|---|
| Follow-up period after hysterectomy, mo | median [range] | 27 [10–55] | 27 [2–103] | 0.48 |
| Vaginal cytology examination per patient, n | mean ± SD | 3.7 ± 1.4 | 4.0 ± 2.9 | 0.67 |
| Patients with abnormal vaginal cytology, n (%) | presumed LSIL | 5 (13.9) | 3 (4.8) | 0.07 |
| | presumed HSIL | 0 | 6 (9.5) | |
| Time from hysterectomy to the first detection of abnormal cytology, mo | median [range] | 19 [4–29] | 12 [4–32] | 0.90 |
| Results of vaginal colposcopy-directed biopsy, n (%) | low-grade VAIN | 1 (2.8) | 3 (4.8) | – |
| | high-grade VAIN | 0 | 3 (4.8) | – |
| | no biopsy | 4 (11.1) | 3 (4.8) | – |
| Management for abnormal vaginal cytology, n (%) | observation | 5 (13.9) | 7 (11.1) | – |
| | laser vaporization for high-grade VAIN | 0 | 2 (3.2) | – |

LSIL, low-grade squamous intraepitherial lesion; HSIL, high-grade squamous intraepitherial lesion; VAIN, vaginal intraepithelial neoplasia.

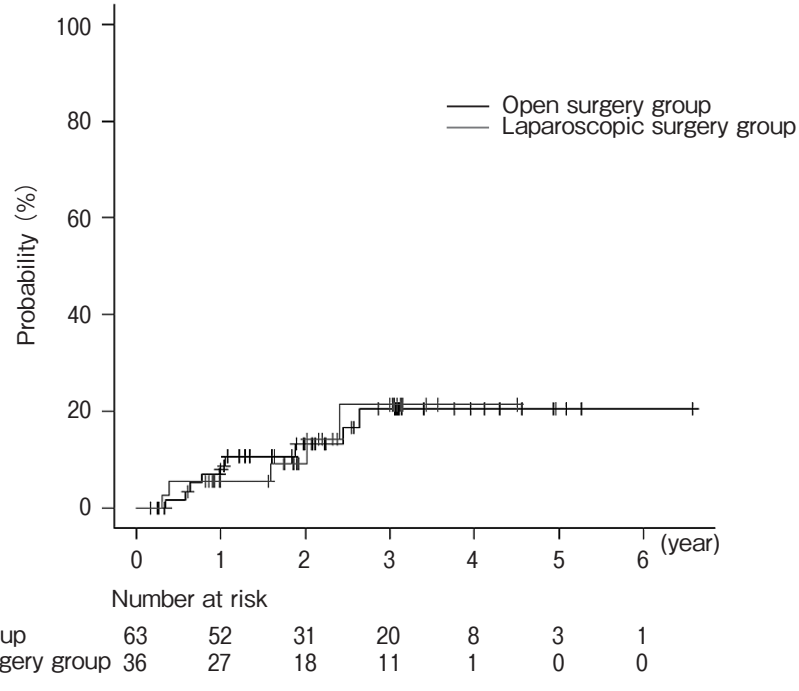


**Fig. 2** Cumulative incidence of abnormal vaginal cytology according to the surgical approach. The cumulative incidence rate at 3 years post-hysterectomy was 21% in the laparoscopic surgery group and 21% in the open surgery group ($p=0.96$). The cumulative incidence did not increase beyond 3 years of postoperative follow-up in either group.

Table 3 Multivariate analysis for the incidence of postoperative abnormal vaginal cytology

| Variables | | n | HR (95%CI) | *P*-value |
|---|---|---|---|---|
| Age at time of hysterectomy | <50 y | 45 | 1 | 0.01 |
| | ≥50 y | 54 | 8.11 (1.73–37.98) | |
| BMI | <25 | 80 | 1 | 0.41 |
| | ≥25 | 19 | 0.42 (0.053–3.29) | |
| History of vaginal delivery | No | 11 | 1 | 0.43 |
| | Yes | 80 | 2.51 (0.25–25.09) | |
| History of abdominal surgery | No | 61 | 1 | 0.23 |
| | Yes | 32 | 2.17 (0.61–7.68) | |
| History of smoking | No | 40 | 1 | 0.48 |
| | Yes | 56 | 1.54 (0.47–5.06) | |
| Surgical approach | Open | 63 | 1 | 0.66 |
| | Laparoscopic | 36 | 1.31 (0.40–4.33) | |

BMI, body mass index; HR, hazard ratio; 95%CI, 95% confidence interval.

lative incidence rates showed no significant difference between the laparoscopic surgery group and the open surgery group, but age >50 years was a potential risk factor for abnormal vaginal cytology in these patients.

VAIN is a precancerous squamous cell carcinoma of the vagina [12]. Low-grade VAIN often goes into remission, but high-grade VAIN has a relatively high risk of progressing to cancer in approx. 11-13% of cases [13]. Invasive carcinoma of the vagina is rare and accounts for approx. 0.5% of all gynecological malignancies in Japan [14,15]. However, patients with advanced vaginal cancer have a poor prognosis, with approx. 50% experiencing recurrence after standard treatment [16]; a recent study indicated that the 10-year survival rate for patients with vaginal cancer did not improve in the 2000s [15]. The length of time from the identification of high-grade VAIN to progression vaginal cancer is relatively long at 10-64 months [1,17-19]. Although the treatment of VAIN is essential to prevent progression, there is currently no established standard treatment, because of its rarity [20]. VAIN is managed in a variety of ways, including no treatment, topical agents, laser transpiration, and vaginal resection [3].

Women with a history of CIN or cervical cancer are at a higher risk of VAIN than those without a history [1] because risk factors for developing VAIN are similar to those for CIN, including high-risk HPV infection, smoking, immunosuppression, and multiple sexual partners [21,22]. VAIN has been reported to occur in 1-10% of patients undergoing a total hysterectomy for CIN, with an increased risk of vaginal cancer for the following 20 years [2,3]. Kim *et al.* investigated the occurrence of VAIN in 374 patients who underwent a hysterectomy for CIN: approx. 90% of the patients underwent a hysterectomy with minimally invasive surgery (MIS), and the remaining 10% underwent an open hysterectomy [3]. The VAIN incidence in their series was 9.6%, with no significant difference in its incidence between the patient groups based on the surgical procedures (MIS vs. open). The only risk factor that Kim *et al.* observed for VAIN incidence was age >50 years, which is consistent with our present finding. However, the details of the MIS in that study were not described [3].

The American Society of Colposcopy and Cervical Pathology recommends that (*i*) vaginal screening should be performed for ≥20 years after a hysterectomy in women with CIN2 or higher disease, and (*ii*) this screening should be performed at ≤1-year intervals in high-risk patients [4]. In the present series of patients, vaginal cytology testing performed at 6- to 12-month intervals had a slightly higher detection rate of 14.1% for abnormal vaginal cytology compared to previous studies; the median time from our patients' hysterectomy to the first detection of abnormal cytology was 13 months, and the cumulative incidence did not increase beyond the 3-year postoperative follow-up. Although the precise incidence of VAIN is unknown in our series because not all of the patients with abnormal vaginal cytology underwent colposcopy-directed biopsies, it seems reasonable to estimate the incidence of VAIN from vaginal cytology results because the sensitivity of vaginal cytology for VAIN is >80% [2,13,23].

Our results suggest that when patients who undergo a hysterectomy for CIN3 also undergo postoperative surveillance that includes vaginal cytology at 6- to 12-month intervals, the follow-up could be completed within 3 years after the hysterectomy if there are no abnormal vaginal cytology findings during the follow-up. However, the median follow-up period after the hysterectomies in the present patients was 27 months, and the possibility that loss to follow-up could affect the incidence of abnormal vaginal cytology should be considered. Further studies are needed to confirm our present findings.

The NHO Shikoku Cancer Center began providing the total laparoscopic hysterectomy procedure in 2016; the longer operative time in the present laparoscopic surgery group compared to the open surgery group may be due to the shorter time since the laparoscopic surgery was introduced in our hospital. Among the well-known risk factors for perioperative complications of total hysterectomy [24,25], a history of abdominal surgery was more common in the present open surgery group, and a history of cervical conization was more common in the laparoscopic surgery group. The estimated blood loss was significantly lower in the laparoscopic surgery group versus the open surgery group, as reported in another study [7]. The histological diagnosis confirmed the complete resection of the cervical lesions in all but one of the present 99 patients; she had a positive margin of the resected uterus. Although a bias in the choice of surgical procedure due to physicians' preferences cannot be ruled out, these results suggest that the factors that could affect the resection of CIN3 lesions were not significantly different between our laparoscopic and open surgery groups.

Age > 50 years was the single positive risk factor for abnormal vaginal cytology identified in this study, which is consistent with earlier reports and demonstrates the association between older age and the occurrence of VAIN [3,5,26]. Although HPV infection is a well-known risk factor for VAIN [21,27], an investigation conducted in Sweden reported that the rate of HPV infection in the uterine cervix or vagina was low at 4.1% among women aged > 60 years [28]. There may thus be other causes involved in the development of VAIN other than HPV infection. Unfortunately, we were unable to determine the HPV infection rate in the present patients or to examine the relationship between high-risk HPV infection and abnormal vaginal cytology. The evidence regarding factors that may be associated with the increased risk of VAIN in elderly women is still limited, and additional studies are needed.

Several study limitations should be acknowledged. This was a retrospective analysis with a small sample size (n = 99) and conducted at a single institution, and the postoperative surveillance interval was determined at each physician's discretion, which may have induced bias that could have affected the results.

In conclusion, the results of this study provide useful information for managing patients after a total laparoscopic hysterectomy for CIN3. Our findings indicated that the laparoscopic approach has no worse implications than the conventional open approach in the development of postoperative abnormal vaginal cytology. As for VAIN surveillance after a total hysterectomy for CIN3, vaginal cytology examinations at 6- to 12-month intervals for 3 years after the surgery seem reasonable; however, careful follow-up is necessary, especially in older patients.

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