Int J Clin Exp Med 2017;10(8):12223-12228
www.ijcem.com /ISSN:1940-5901/IJCEM0059018

Original Article

Feasibility and efficacy of vaginectomy for patients with vaginal vault high-grade squamous intraepithelial lesion after hysterectomy: a retrospective analysis of 52 cases

Mingzhi Zhao, Jianfeng Zhang, Guoqian Wei, Changdong Hu, Zhiling Zhu

Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China

Received June 8, 2017; Accepted June 30, 2017; Epub August 15, 2017; Published August 30, 2017

Abstract: Objective: Vaginal vault high-grade squamous intraepithelial lesion (HSIL) after hysterectomy is sometimes seen and the treatment is tricking. We retrospectively analyzed the feasibility and efficacy of vaginectomy in these cases. Methods: Fifty-two cases diagnosed with vaginal HSIL after hysterectomy underwent partial or total hysterectomy in our hospital with complete follow-up were included. The patients' demographics, perioperative profiles, pathological findings, human papilloma virus (HPV) infection and postsurgical changes as well as long-term outcomes were collected and analyzed. Results: Both partial and total vaginectomy could be performed in these patients with acceptable blood loss (range: 5-1500 mL), operation time (range: 23-580 minutes) and low incidence of postoperative complications (5.77%). Postoperative pathological examinations found 15 cases were with invasive carcinoma. After surgery, there was a decrease in the positive rate of HPV infection. The recurrence rate (15.38%) was low during the follow-up. There was no significant difference between patients with partial vaginectomy and those with total vaginectomy in operation time (P=0.149), recurrence (P=0.870) or the median time to HPV negativity (P=0.660). Total vaginectomy was associated with more estimated blood loss compared with partial vaginectomy (P=0.016). Conclusion: Vaginectomy for vaginal HSIL after hysterectomy was necessary and feasible. Both partial and total vaginectomies were related with low incidence of recurrence and reduced HPV positivity.

Keywords: Vaginectomy, high-grade squamous intraepithelial lesion, vaginal intraepithelial neoplasia, cervical neoplasia

Introduction

Vaginal intraepithelial neoplasia (VaIN) once thought rare, is increasingly reported with the application of cytology screening and colposcopy for patients with abnormal cervical cytology [1]. In patients with hysterectomy due to cervical neoplasia and other uterus appendages diseases, the risk of VaIN increased and more cases have been reported [2]. Li et al. found that 15% of 147 patients treated for invasive cervical carcinoma were diagnosed with VAIN during the 1 to 139 months' follow-up [3]. Jentschke et al. further reported that about two thirds of the VAIN cases occurred after hysterectomy [4]. These results suggested more emphasis should be laid on the screening and treating of VAIN after hysterectomy.

Traditionally, VaIN is classified to 3 degrees with VaIN 1 and 2 involve the lower one-third and two-thirds of the epithelium respectively, and VaIN 3 involving more than two-thirds of the epithelium or carcinoma in situ. This classification system is replaced by a two-tier system of low- and high-grade squamous intraepithelial lesions (LSIL or HSIL, respectively) since 2012 [5]. LSIL includes lesions as condyloma and VaIN I which probably regress without any treatment in about 90% of cases [6]. HSIL replaces the VaIN II/III category and have a tendency to progression to invasive vaginal cancer [4]. Once HSIL is confirmed, individualized treatment should be considered [7].

No standard treatment for HSIL after hysterectomy hasbeen set up. The reported strategies include medication (imiquimod, 5-Fluorouracil and et al.), focal ablation or excision, cavitational ultrasonic surgical aspiration, partial upper vaginectomy or total vaginectomy and radiotherapy [8]. Of them, brachytherapy is highly effective, but cannot provide a specimen for detailed pathological diagnosis. Vaginectomy is

Table 1. Patient characteristics across partial or total vaginectomy

	Partial upper vaginectomy (n=37)	Total vaginectomy (n=15)	*P* value
Age (mean ± sd, (range), year)	52.74±1.46 (37-71)	57.50±2.78 (40-69)	0.130
Time from hysterectomy to HSIL diagnosis (mean ± sd, (range) months)	44.47±6.33 (3-122)	37.20±9.52 (5-74)	0.573
Indication of previous hysterectomy (benign uterine diseases/endometrial neoplasms/cervical intraepithelial neoplasia/cervical carcinoma)	4/1/26/6	0/0/14/1	0.447

Table 2. Perioperative profiles and postoperative complications in patients undergoing partial or total vaginectomy

	Partial upper vaginectomy (n=37)	Total vaginectomy (n=15)
Surgical approach (trans-vaginally/laparoscopically)	24/13	8/7
Double-J stents insertion	9 (24.3%)	9 (60.0%)
Vaginal reconstruction	0	1 (6.67%)
Operation time (median, (range), min)	95 (23-275)	114 (56-580)
Estimated blood loss (median, (range), min)*	50 (5-450)	100 (50-1500)
Postoperative complications (urinary or bladder injury/intestinal injury/infection)	2/0/1	0/0/0

Note: *P<0.05; partial upper vaginectomy vs total vaginectomy.

radical, permits pathological confirmation and is more advisable if multifocal lesions, a feature of VAIN, existed [9, 10]. Case reports disclaimed that laparoscopic upper vaginectomy for post-hysterectomy HSIL was plausible and safe [7]. We have performed 15 total vaginectomies and 37 partial upper vaginectomies since Jan. 2013 and the efficacy was summarized.

Methods

Case selection

This retrospective study was conducted after getting approval from the ethical committee of Obstetrics and Gynaecology Hospital of Fudan University and informed consent from patients. From Jan. 1st, 2013 to Jan. 30th, 2017, cases with partial or total vaginectomy due to HSIL after hysterectomy were identified. HSIL was diagnosed through punch biopsy. The cases were included for retrospective analysis if regular follow-up were conducted after surgery at a 2-week interval for at least three months and HPV infection types were examined. Cytology and HPV DNA tests using HC2 HR HPV kits and Cobas 4800 HPV kits [11, 12] should be performed before surgery and every 3 months postoperatively. The surgical methods, partial or total vaginectomy, were chosen based on the sites of HSIL. After surgery, the samples should undergo pathological examination. Patients with inadequate information or no HPV infection screening were ruled out.

Data collection

After reading the medical files and follow-up records, the following patients information were collected: age, the time and reason of previous hysterectomy, HPV infection types at the time of vaginectomy, pathological findings, perioperative parameters including the duration of surgery, estimated blood loss and surgical procedures, postoperative complications, the length of follow-up, HPV infection status and recurrence after surgery.

Outcome measures

The main goal of this study was to explore the efficacy and feasibility of vaginectomy for patients with HSIL after hysterectomy. The main outcome measures included perioperative parameters, incidences of postoperative complications and recurrence after surgery. The secondary outcome measures included HPV infection changes after surgery and the median time to HPV reversion.

Statistical analysis

Statistical analysis was performed using the SPSS 20.0 software package. Continuous data

were expressed as mean ± standard deviation (mean ± sd) and one-way ANOVA was used to detect the differences between partial vaginectomy and total vaginectomy if homogeneity of variance and normal distribution assumed. Otherwise, the data were shown as median (range) and non-parametric Kruskal-Wallis test (homogeneity of variance or normal distribution not assumed) was used to detect surgical method related differences. Dichotomous data were expressed as incidence or percent and Chi-squared test was used to test the differences between partial vaginectomy and total vaginectomy. The median time to HPV conversion was calculated using the survival analysis method. A *P* value smaller than 0.05 was considered statistically significant.

Results

Patient characteristics

There were 37 patients undergoing partial vaginectomy and 15 cases receiving total vaginectomy due to HSIL after hysterectomy. The ages ranged from 37 to 71 years old with an average of 54.3 years old. The reasons for previous hysterectomy included benign uterine diseases (n=4), endometrial neoplasms (n=1), cervical intraepithelial neoplasia (n=40) and cervical carcinoma (n=7). The time from hysterectomy to HSIL ranged from 3 to 122 months. The patients' characteristics across different vaginectomy methods were shown in **Table 1**. There was no significant difference in the age, time from hysterectomy to HSIL diagnosis or indication of previous hysterectomy between partial or total vaginectomy groups (all P>0.05).

Perioperative profiles, postoperative complications and recurrence

As shown in **Table 2**, all of the surgeries were successfully finished. The surgeries were performed either trans-vaginally (n=32) or laparoscopically (n=20). Double-J stents were inserted into both sides of ureter to prevent ureter injury in 18 cases. One patient received vaginal reconstruction after total vaginectomy. There was no difference in operation time (P=0.149) between partial and total vaginectomy and estimated blood loss [13] was greater in patients undergoing total vaginectomy compared with those receiving partial vaginectomy (P=0.016). The estimated blood loss ranged from 5 to 1500 mL. Only one case who underwent enlarged radical resection due to intraoperative pathological confirmation of invasive cancer accepted blood transfusion and her estimated blood loss was 1500 mL.

The duration of postoperative follow-up ranged from 4 to 45 months with a median of 21 months in patients with partial vaginectomy and 17 months in patients with total vaginectomy (P=0.079). During the phase of follow-up, urinary or bladder injuries were found in 2 (5.4%) cases with partial vaginectomy. No intestinal damage was identified. One patient undergoing partial vaginectomy was fund to have pelvic floor abscesses 1 year after the operation, and she was cured by incision and antibiotic therapy. Recurrent rates were 13.51% (5/37) for partial vaginectomy and 20% (3/15) for total vaginectomy (P=0.870).

Pathological findings

Before surgery, all the 52 patients were diagnosed with HSIL. During the operation, fast frozen pathology was performed in 41 cases and 3 were found to be with invasive carcinoma. Postoperative pathological examination was performed for all patients and 15 cases were diagnosed with invasive carcinoma. The resection margins were all negative for malignancy including 27 cases with disease-free margin, 3 cases with LSIL, 22 cases with HSIL. The pathological finds were summarised in **Figure 1**.

HPV tests and postoperative HPV infection reversion

Pre-operative HPV infection screening found that 44/52 cases were found to be affected HPV. Further examination using Cobas 4800 HPV kits found that HPV 16 infection occurred in 56.8% of the cases and HPV 18 was identified in 3 cases. The HPV infection results across different surgical methods were shown in **Figure 2**. The HPV types distribution was similar in patients undergoing partial and total vaginectomy (P=0.630).

After surgery, the median time for patients with partial or total vaginectomy to achieve HPV negativity were 12 and 9 months respectively with no significant difference (P=0.660, **Figure 3**).

Discussion

In this retrospective study, we found that vaginal HSIL after hysterectomy was related with

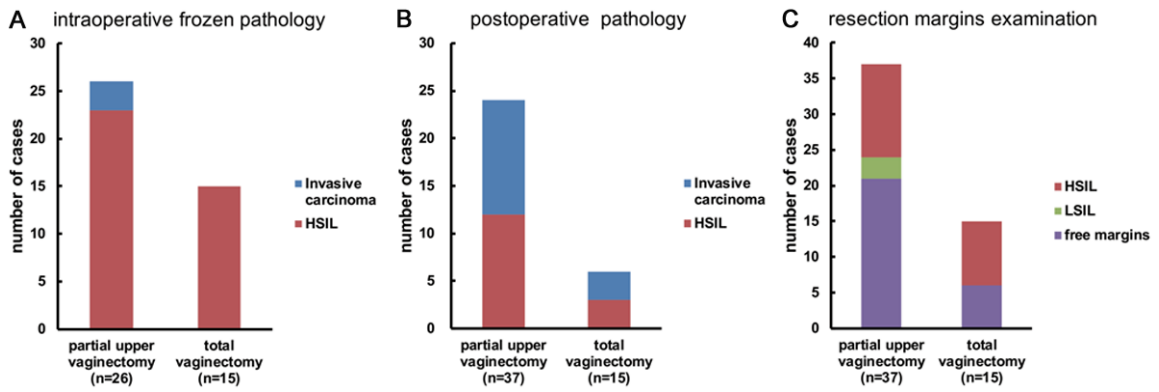

Figure 1. Intraoperative and postoperative pathological findings of the 52 cases undergoing vaginectomy due to high-grade squamous intraepithelial lesions (HSIL). A. Froze section examination results before vaginectomy. B. Postoperative paraffin section examination results. C. Postoperative resection margin examination results.

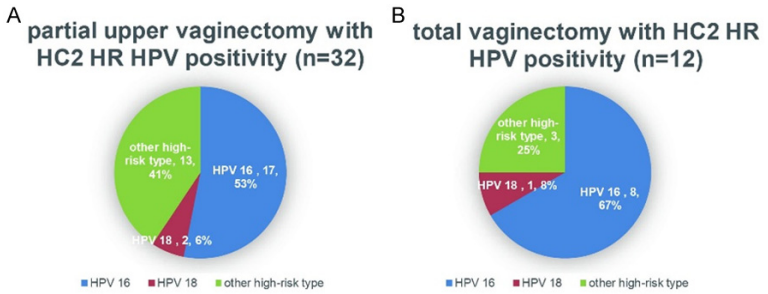

Figure 2. Detailed results of the Cobas 4800 HPV test in cases with HC2 HR HPV test positivity. A. Cases with partial vaginectomy. B. Cases with total vaginectomy.

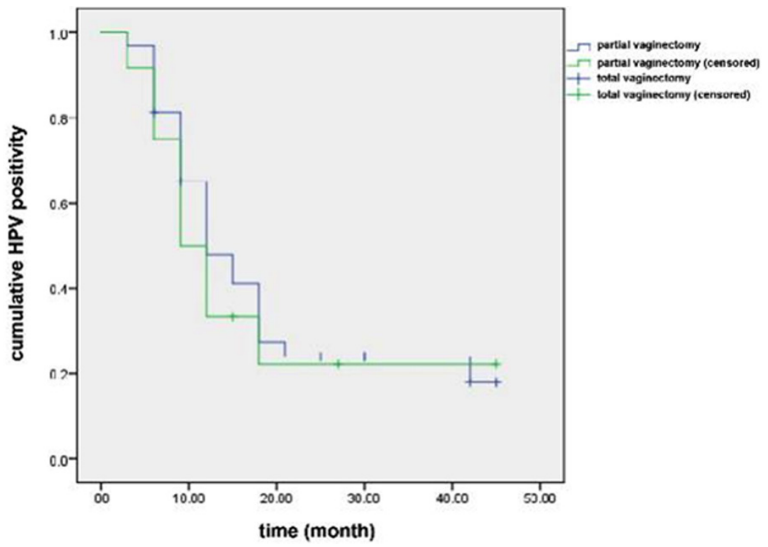

Figure 3. HPV infection conversion after partial and total vaginectomy. There was no significant difference in the median time achieve 50% HPV infection negativity.

invasive carcinoma; partial and total vaginectomy for patients with vaginal HSIL after hysterectomy was safe and feasible; vaginectomy could reduce the rate of HPV infection and was related with low incidence of recurrence and there was no difference in clinical efficacy between partial and total vaginectomy.

The necessity of partial or total vaginectomy for vaginal HSIL after hysterectomy

Studies have found that patients with a history of CIN or cervical cancer were more likely to develop HSIL in the vaginal vault than normal control [1]. Moreover, it was reported that more than two thirds of vaginal HSIL cases had a history of hysterectomy [14-16]. In our study we further found that more than 90% of the HSIL cases were accompanied with hysterectomy due to CIN or cervical tumour (**Table 1**). These results suggested a much higher incidence of vaginal HSIL after hysterectomy, especially hysterectomy due to CIN or cervical cancer.

The phenomenon might be a consequence of the high-risk HPV infection and surgery related with lesions. We found that more than 80% of the enrolled cases were diagnosed to

have HPV infection. This finding was similar to results from Chen et al. [17]. Furthermore, as HPV infection was closely related with cervical neoplasm, the concurrent vaginal HSIL and HPV infection were very dangerous and should be treated timely [4]. Our postoperative pathology found about one third of the cases probably had invasive carcinoma (**Figure 1**). These results were similar reports from Hoffman et al. who discovered that 28% of occult invasive cancer among 32 patients who underwent upper vaginectomy for VAIN 3 [18]. Taken together, these findings highlighted the necessity of vaginectomy for vaginal HSIL after hysterectomy.

Safety and feasibility of vaginectomy for vaginal HSIL after hysterectomy

Surgical resection is a radical treatment method. However, as the vagina is located close to the bladder and rectum, surgery is considered very difficult and related with high-risk of postoperative complications [10]. In 2013, a Korean scholar firstly reported that laparoscopic upper vaginectomy for post-hysterectomy HSIL and superficially invasive vaginal carcinoma was feasible [7]. Then a case report stated that total vaginectomy to refractory VAIN III or suspected cancer was feasible [10]. Similar to these results, our retrospective study found that both partial and total vaginectomy was feasible for vaginal HSIL after hysterectomy. The surgical duration and bloods loss was tolerable. Although total vaginectomy was accompanied with greater blood loss, it also fell in our expectations and preparations. Furthermore, we found a low incidence of postoperative complications which further confirmed the safety of vaginectomy.

Efficacy ofvaginectomyfor vaginal HSIL after hysterectomy

We found that vaginectomy for vaginal HSIL after hysterectomy was accompanied with a recurrence rate of 15.4% which suggested that vaginectomy was highly effective. Several treatment options were available for vagina HSIL. Dodge et al. used laser vaporization and reported a cure rate of only 61%. They further found that 5-FU topical injection was only with a cure rate of just 40% [19]. In contrast, in a retrospective study of 52 patients treated by laser ablation and vaginectomy, Diakomanolis et al. found that vaginectomy was related with a cure rate of 80% while laser ablation yielded a cure rate of 68% [20]. Hoffman et al. further found that upper vaginectomy for VAIN was related with a cure rate of 82% [18]. In addition, Indermaur et al. reported a cure rate of 88% in 105 patients undergoing upper vaginectomy due to VAIN [16]. Taken together, surgical vaginectomy for vaginal HSIL after hysterectomy was effective. Besides the cure rate and recurrence, we further found that after surgery, the HPV infection rate gradually decreased (**Figure 3**), suggesting an efficacy of vaginectomy in controlling HPV spreading.

Limitations and caveats

There were two limitations should be considered when interpreting our results. First, although we only included patients with steady follow-up, the length of follow-up differed greatly which imposed a great obstacle on estimating clinical efficacy and HPV infection changes. Secondly, we could not get the full reasons for choosing partial or total vaginectomy. A better treatment method should consider all the following questions including the number of lesions, treatment history, and the doctor's and patient's preferences. We cannot make sure that the current surgical method was reasonable enough. Future prospective studies with regular follow-up would be helpful to further determine the efficacy and safety of surgical resection for vaginal HSIL after hysterectomy.

In conclusion, our retrospective analysis supported that both partial and total vaginectomy for vaginal HSIL after hysterectomy was safe, feasible and efficacious.

Disclosure of conflict of interest

None.

Address correspondence to: Zhiling Zhu, Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, No.128 Shenyang Road, Shanghai 200090, China. Tel: +86-021-63450944; Fax: +86-021-63450944; E-mail: Mingzhizhao@icloud.com

References

[1] PPC Ip and KY Tse. Vaginal intraepithelial neoplasia. Springer International Publishing 2016; 36: 232-239.

[2] Wang Y, Kong WM, Wu YM, Wang JD and Zhang WY. Therapeutic effect of laser vaporization for

vaginal intraepithelial neoplasia following hysterectomy due to premalignant and malignant lesions. J Obstet Gynaecol Res 2014; 40: 1740-1747.
[3] Li Z, Barron S, Hong W, Karunamurthy A and Zhao C. Surveillance for recurrent cancers and vaginal epithelial lesions in patients with invasive cervical cancer after hysterectomy: are vaginal cytology and high-risk human papillomavirus testing useful? Am J Clin Pathol 2013; 140: 708-714.
[4] Jentschke M, Hoffmeister V, Soergel P and Hillemanns P. Clinical presentation, treatment and outcome of vaginal intraepithelial neoplasia. Arch Gynecol Obstet 2016; 293: 415-419.
[5] Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ and Wilbur DC. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American society for colposcopy and cervical pathology. J Low Genit Tract Dis 2012; 16: 205-242.
[6] Rome RM and England PG. Management of vaginal intraepithelial neoplasia: a series of 132 cases with long-term follow-up. Int J Gynecol Cancer 2000; 10: 382-390.
[7] Choi YJ, Hur SY, Park JS and Lee KH. Laparoscopic upper vaginectomy for post-hysterectomy high risk vaginal intraepithelial neoplasia and superficially invasive vaginal carcinoma. World J Surg Oncol 2013; 11: 126.
[8] Frega A, Sopracordevole F, Assorgi C, Lombardi D, V DES, Catalano A, Matteucci E, Milazzo GN, Ricciardi E and Moscarini M. Vaginal intraepithelial neoplasia: a therapeutical dilemma. Anticancer Res 2013; 33: 29-38.
[9] Zolciak-Siwinska A, Gruszczynska E, Jonska-Gmyrek J, Kulik A and Michalski W. Brachytherapy for vaginal intraepithelial neoplasia. Eur J Obstet Gynecol Reprod Biol 2015; 194: 73-77.
[10] Youn JH, Lee MA, Ju W, Kim SC and Kim YH. Total vaginectomy for refractory vaginal intraepithelial neoplasia III of the vaginal vault. Obstet Gynecol Sci 2016; 59: 71-74.
[11] Lee DH, Hwang NR, Lim MC, Yoo CW, Joo J, Kim JY, Park SY and Hwang SH. Comparison of the performance of Anyplex II HPV HR, the Cobas 4800 human papilloma virus test and Hybrid Capture 2. Ann Clin Biochem 2016; 53: 561-567.
[12] Heideman DA, Hesselink AT, Berkhof J, van Kemenade F, Melchers WJ, Daalmeijer NF, Verkuijten M, Meijer CJ and Snijders PJ. Clinical validation of the cobas 4800 HPV test for cervical screening purposes. J Clin Microbiol 2011; 49: 3983-3985.
[13] Guinn NR, Broomer BW, White W, Richardson W, Hill SE. Comparison of visually estimated blood loss with direct hemoglobin measurement in multilevel spine surgery. Transfusion 2013; 53: 2790-2794.
[14] Ferris DG, Messing MJ and Crosby JH. Vaginal intraepithelial neoplasia III detected after hysterectomy for benign conditions. J Fam Pract 1995; 40: 81-85.
[15] Kalogirou D, Antoniou G, Karakitsos P, Botsis D, Papadimitriou A and Giannikos L. Vaginal intraepithelial neoplasia (VAIN) following hysterectomy in patients treated for carcinoma in situ of the cervix. Eur J Gynaecol Oncol 1997; 18: 188-191.
[16] Indermaur MD, Martino MA, Fiorica JV, Roberts WS and Hoffman MS. Upper vaginectomy for the treatment of vaginal intraepithelial neoplasia. Am J Obstet Gynecol 2005; 193: 577-580; discussion 580-571.
[17] Chen L, Hu D, Xu S, Wang X, Chen Y, Lv W and Xie X. Clinical features, treatment and outcomes of vaginal intraepithelial neoplasia in a Chinese tertiary centre. Ir J Med Sci 2016; 185: 111-114.
[18] Hoffman MS, DeCesare SL, Roberts WS, Fiorica JV, Finan MA and Cavanagh D. Upper vaginectomy for in situ and occult, superficially invasive carcinoma of the vagina. Am J Obstet Gynecol 1992; 166: 30-33.
[19] Dodge JA, Eltabbakh GH, Mount SL, Walker RP and Morgan A. Clinical features and risk of recurrence among patients with vaginal intraepithelial neoplasia. Gynecol Oncol 2001; 83: 363-369.
[20] Diakomanolis E, Rodolakis A, Boulgaris Z, Blachos G and Michalas S. Treatment of vaginal intraepithelial neoplasia with laser ablation and upper vaginectomy. Gynecol Obstet Invest 2002; 54: 17-20.