

Should we search for high-risk HPV in vaginal vault Pap smear after hysterectomy due to CIN2+?

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Summary

Women with a history of hysterectomy due to malignant or premalignant cervical disease are currently submitted to tight surveillance, which consists of vaginal Pap tests for as long as 20 years in the late follow-up period. Nevertheless, published literature has concluded that vaginal Pap screening has a very low detection yield. Also, these recommendations are almost entirely from an era before high-risk HPV (hrHPV) DNA testing. The authors' aim is to review these women's current management and share the scarce recommendations available for the management of abnormal vaginal Pap and/or adjunctive hrHPV DNA tests in these patients.

Key words: Vaginal Pap tests; hrHPV vaginal testing; Follow-up; Hysterectomy; CIN2+.

Introduction

Every year about 13,000 women are diagnosed with cervical cancer, half of them being diagnosed with Stage I disease [1]. Recently, the algorithm for the diagnosis of cervical cancer has changed, mostly due to the introduction of co-testing with both cytology and high-risk HPV (hrHPV) in women over 30 years of age [2]. This has been recommended by all major cervical cancer screening societies throughout the globe, as well as the Portuguese Society for cervical cancer screening [3-7]. The appropriate treatment for women with early stage cervical cancer consists of total or radical hysterectomy with pelvic lymphadenectomy and radiation, providing these patients with a five-year survival rate that exceeds 90% [2]. The scar left on the vaginal vault after hysterectomy is a site with increased risk for vaginal cancer, and therefore the Society for Gynecologic Oncology (SGO) and the American College of Obstetricians and Gynecologists (ACOG) recommend physical examination and annual cytologic surveillance for 20 years after hysterectomy for cervical intraepithelial neoplasia grade 2+ (CIN2+) [8, 9]. This was based on data collected from long-term follow-up studies in this population of women, which showed an elevated rate of invasive disease when compared with the general population until at least 20 years after treatment [5]. This surveillance can also be important in the early diagnosis of local recurrences, present in 10% to 20% of cases, and which respond to salvage treatments with potential cure [2].

This tropism for the vaginal epithelia may be explained by the same embryological origin of the upper vagina and cervix, and the observation of synchronous or metachronous HPV-related cervical lesions with vaginal intraepithelial neoplasia (VaIN) or vaginal invasive cancer

[2,10]. Although this correlation between VaIN and HPV infection has long been known, the role which hrHPV testing might have in women with invasive cervical cancer after hysterectomy is still not clear [2]. Also, the recommendation for long-term annual screening with vaginal cytology after hysterectomy in this population of women was made prior to the introduction of hrHPV testing [5]. To the present authors' knowledge, there are currently no specific guidelines that could help clinicians manage abnormal vaginal Pap test results in this population, as well as there being no recommendations on adjunctive hrHPV DNA testing on vaginal cytological specimens. In fact, adaptation of the published guidelines for cervical cancer screening seems to be the usual course of action among gynaecologists who work in this area [11]. Therefore, the aim of this article is to review the literature regarding the role of hrHPV DNA testing on vaginal cytology performed in hysterectomised women due to CIN2+, and try to provide the reader with the most recent data and recommendations.

Discussion

Vaginal cancer is an uncommon gynaecological malignancy related to HPV, accounting for 1–4% of cancers of the female genital tract [9, 12]. Squamous cell carcinoma is the main histological type of primary vaginal cancer (80–90%); adenocarcinomas and melanomas are diagnosed less frequently [9, 12]. Analogous to high-grade squamous intraepithelial lesion (HSIL)/cervical intraepithelial neoplasia (CIN) grades 2/3, vaginal cancer is also preceded by its premalignant lesion, VaIN which is characterised by the presence of squamous cell atypia without invasion [9, 10]. VaIN lesions are classified according to the depth of epithelial involvement, always without stromal invasion: invasion of

Table 1. *Recommendations for follow-up on women hysterectomised due to CIN2+ by the NHS/UK guidelines on cervical cancer screening.*

Premalignant or malignant lesion which motivated hysterectomy	Follow-up
Completely excised CIN after hysterectomy	Vaginal vault cytology at 6 and 18 months after hysterectomy
Incompletely excised CIN after hysterectomy	Follow-up should be as if their cervix remained in situ – continue until 65 years or ten years after surgery (whichever is later)
CIN 1	Vault cytology at 6, 12 and 24 months
CIN 2/3	Vault cytology at 6 and 12 months, followed by 9 annual vault cytology samples

Table 2. *Recommendations for follow-up on women hysterectomised due to CIN2+ by the Cancer Council Australia Cervical Cancer Screening Guidelines Working Party.*

Premalignant or malignant lesion which motivated hysterectomy	Follow-up
Total hysterectomy after completed test of cure* (women with a history of HSIL who have completed test of cure and with no evidence of cervical pathology on surgical specimen)	No follow-up necessary
Total hysterectomy after histologically confirmed HSIL without test of cure	Vaginal vault co-test 12 months after treatment and annually thereafter until completion of test of cure
Total hysterectomy after adenocarcinoma in situ	Vaginal vault co-test 12 months and annually thereafter, indefinitely
Total hysterectomy for treatment of CIN2+ (irrespective of cervical margins)	Vaginal vault co-test 12 months after treatment and (irrespective of cervical margins) annually thereafter until completion of test of cure
Any positive co-test result following total hysterectomy (positive oncogenic HPV (any type) test result and/or any cytological abnormality)	Colposcopic assessment
Total hysterectomy after genital tract cancer	Surveillance from a gynaecological oncologist (cervical or endometrial cancer)

*Test of cure: two consecutive negative co-testing results during annual co-testing.

the lower one- and two-thirds of the epithelium correspond to VaIN 1 and 2, respectively. Invasion of more than two-thirds and of the whole epithelial thickness are attributed to VaIN 3 and carcinoma in situ, respectively [10, 12]. VaIN 1 is a transient, benign manifestation of HPV infection [9]. VaIN 3 is the epithelial lesion with the highest potential of progression to vaginal cancer, and is considered a “high-grade VaIN” (HG-VaIN) lesion. The VaIN2 category is not reproducible among pathologists, and has a hypothetical intermediate risk of progression to vaginal cancer [12].

Both vaginal carcinoma and VaIN are uncommon. The first has an annual incidence of 0.69 per 100,000 women; VaIN has an even lower reported incidence, of 0.2 to 0.3 per 100,000 women/year [9, 10]. These low incidences justify the recommendations made for hysterectomised women with no history of CIN2+ not to be screened for vaginal can-

cer using any modality. In fact, evidence shows that only 1.1% to 1.8% of vaginal cuff cytology tests in this group of women were abnormal, and none progressed to vaginal cancer [2, 5]. Other studies stated that the incidence of VaIN in these women was 1.3% in ten years [10]. However, the story is a little different when it comes to women hysterectomised due to CIN2+ [12]. These women are at an increased risk of VaIN or vaginal cancer due to persistent hrHPV infection, with the literature reporting VaIN in approximately 6–10% of cases [2, 5, 9, 11, 13]. Another study including 33 patients hysterectomised for CIN2+ or carcinoma stated that 70% had VaIN lesions [14]. This phenomenon may be due to incomplete excision of a contiguous, pre-existing intraepithelial lesion, multicentric intraepithelial lesions, recurrent lesions due to the persistence of HPV infection, or new intraepithelial lesions following

a new HPV infection [11]. Although the rate of progression to cancer in VaIN lesions (grades 1, 2, and 3) is much lower than for that reported for CIN3 (0–9% *vs* 30%, respectively), these women are considered to be at higher risk of developing a vaginal cancer, and therefore the recommendations are to perform a yearly vaginal cytology [9, 12].

HPV infection of the cervix, with its known carcinogenic potential, is as common as HPV infection of the vagina [9]. HPV is present in 98–100% of VaIN1 lesions, 90–92.5% in VaIN 2–3 and 65–70% of vaginal invasive carcinomas [15]. HG-VaIN lesions are related to HPV 16 and 18 in 64% of cases, and these hrHPV types are present in 72% of women with vaginal cancer [10]. This confirms the similar affinity of hrHPV for vaginal epithelia, when compared to its affinity to the cervix [16].

In a worldwide study including 189 VaIN2/3 and 408 invasive vaginal cancer cases individually tested for HPV, the global HPV positivity was 96% in VaIN2/3 and 74% in vaginal cancer [17]. In most studies, HPV 16 was most widely associated with VaIN and vaginal cancer; hrHPV types HPV18, 31, 33, and 52 were also very common, although showing a much lower prevalence than HPV 16 [9]. Finally, to highlight the fact that the types of hrHPV do not differ much in cervical and vaginal cancer, a study by Castle et al. compared HPV prevalence among hysterectomised women and those who had not been hysterectomised, and they found no significant differences in high-risk HPV between groups (4.5% in hysterectomised *vs.* 6.5% in non-hysterectomised women) [18].

Due to the rarity of vaginal cancer, professional society guidelines unanimously recommend against vaginal cancer screening using vaginal Pap tests in hysterectomised women for benign disease [9]. Vaginal Pap tests are currently only recommended for vaginal cancer screening of women who have had hysterectomies and prior diagnosis of malignant or premalignant lower genital tract disease [11].

In fact, the literature consistently documents very low positive predictive value (PPV) for vaginal cytology, and therefore its low chance of detecting abnormalities after hysterectomy for benign disease [4, 19]. A systematic review gathered data from 19 studies, and divided hysterectomised women between two groups: women with no history of CIN ($n = 6,543$) and women with a history of CIN ($n = 5,037$). The first group showed a 1.8% rate of abnormal vaginal cytology screening result, and 0.12% presented with vaginal intraepithelial neoplasia on biopsy. There were no reported cases of cancer [3]. This leads to the recommendation that vaginal cancer screening in these women is not effective and will cause anxiety and overtreatment [19]. Another study by Pearce et al. consists of one of the largest cohorts of examined vaginal cytology results following hysterectomy due to benign gynaecological conditions; a total of 9,610 vaginal cytology samples obtained from 5,682 women. Only 104 (1.1%) were abnormal, consisting of 0.5% atypical squamous cells of undetermined significance (ASC-US), 0.5% low-grade squamous intraepithelial

lesion (LSIL), 0.1% HSIL, and 0.02% squamous cell carcinoma (SCC). There were no reported vaginal cancers and only six cases of VaIN1/2. Vaginal cytology had a PPV of 0% for VaIN3 and vaginal cancer and 6.3% for VaIN1/2 [20]. Also, it is not known whether the detection of these cases improved clinical outcomes [4].

Several findings provide evidence to support ongoing surveillance for hysterectomised women with a history of CIN2+, but consider screening using cytology alone [5]. One of the most important meta-analyses to support this was performed by Soutter et al., who evaluated 26 cohorts of women who had been treated for CIN, including four cohorts who were hysterectomised. No significant difference was found regarding the incidence of invasive recurrence between the series of hysterectomised women and those treated with conservative methods of treatment (ablation or excision). Hence, it was concluded that follow-up for women after hysterectomy for CIN2+ and women treated conservatively should be the same [21]. Another recent study compared results of vaginal cytology in three groups of hysterectomised women: one due to cervical cancer; other for CIN3, and the last for benign gynaecological pathology. VaIN2+ lesions could be detected earlier by vaginal cytology in 7.1%, 3.0%, and 0.5% of cases, respectively [22]. However, the literature states that vaginal cytologic evaluation has a consistently low yield, detecting recurrent disease only in 0–17% of cases [8, 23]. In fact, clinical symptoms and physical examination will detect most cases of local recurrent cancer [2]. Other studies found that vaginal vault cytology does not add significantly to physical examination in detecting early disease recurrence, and is rarely the only abnormality in the holistic evaluation of the patient [8]. Vaginal cytology may also be inaccurate in detecting locally persistent or recurrent disease in the early postradiotherapy period due to ambiguous cell morphology after radiation [24]. This has led to recommendations by investigators to abandon vaginal cytology or to limit its use to once a year. However, it is also recommended that an abnormal cytology result suggesting the possibility of vaginal neoplasia warrants colposcopic evaluation and directed biopsy for histologic confirmation [25]. Some authors also suggest that the yearly vaginal Pap smear should be limited to the first five years after treatment without recurrence [26]. Orr et al. found no cases of cancer in the 61 women studied for recurrence with vaginal Pap smears for 143 months after the five-year period of active surveillance, confirming the futility of Pap testing during this period [27].

Due to its rarity, vaginal cancer screening is not recommended in the general population. Therefore, the accuracy value of vaginal cytology for prediction of VaIN2/3 is limited to the few available studies, which state that it has a sensitivity of 83% and a PPV of 0–14% [9]. Bansal et al. gathered data from 2,892 hysterectomised women who underwent vaginal cytology and HPV testing over four years. Squamous cell abnormalities were found in 45.6% of the

cytologic specimens, the majority composed by ASC-US, 5.1% LSIL; 3% atypical squamous cells cannot rule out high-grade (ASC-H), and 1% HSIL. They found that 14.6% of women with LSIL had VaIN2/3, and the remainder were diagnosed with VaIN1 [11]. However, all these findings related to vaginal Pap smear are becoming less relevant to all major societies, who are now making a switch on cervical cancer surveillance based on co-testing (HPV and liquid based cytology) [5].

Recent studies suggest that HPV detection may improve the prognosis of patients treated for cervical cancer because it detects the therapeutic response of the patient, as well as the risk of developing a new cervical or vaginal cancer [28]. Other studies with patients treated with radiotherapy have made it clear that hrHPV DNA persistence is also a predictor for recurrence after therapy [24]. In fact, some authors suggest that tumour cells infected with HPV may persist for several years in a silent status in the residual vaginal epithelia after radical surgery, surviving even in the absence of the transitional zone of the cervix [29].

After FDA approval in April 2014 of the first HPV DNA test for primary cervical cancer screening, the importance of this tool in the diagnosis of both preinvasive and invasive cervical cancer has been undeniable [30]. Furthermore, HPV testing has been also considered a method of post-treatment surveillance of cervical cancer in non-hysterectomised women [24]. However, the data that supports vaginal screening recommendations is still from an era before widespread hrHPV DNA testing [11]. This is confirmed by the recommended cautions on the package of the most widely used hrHPV DNA test, which specifically state that it has not been evaluated in vaginal specimens from patients who have had hysterectomies [31].

The published data on HPV test results in vaginal Pap specimens are scant [11]. One study examined 47 women who underwent hrHPV testing during follow-up of invasive cervical carcinoma treated by hysterectomy. Eleven (23.4%) had at least one positive hrHPV testing. Patients with a hrHPV-positive result had a significantly higher VaIN detection rate when compared with women with a hrHPV-negative result (54.5% vs. 16.7%, respectively). This study underlines a significantly increased detection rate of VAINs in the hrHPV-positive group, which may suggest that the combination of vaginal cytology and HPV co-testing could be an effective detection method in hysterectomised women due to CIN2+ [2]. To the present authors' knowledge, there is only one prospective cohort study examining hrHPV prevalence and its relation to VaIN and vaginal cancer. The majority of women included (728/830) had had hysterectomy for a gynaecologic malignancy, and were a high-risk population for vaginal cancer. VaIN was reported in 5.3% of the study population, and all tested hrHPV-positive (91% for HPV16 and 9% for HPV18). During a three-year follow-up period, 2/5 women with VaIN3 progressed to cancer. In this study, hrHPV testing showed a sensitivity of 90%, specificity of 78%, PPV of 56%,

and negative predictive value (NPV) of 92% for persistence/progression of VaIN [32]. This shows that hrHPV testing in hysterectomised women due to CIN2+ may help to identify VAIN persistence/progression to vaginal carcinoma before cytology becomes abnormal [9]. Other studies also suggest that a negative hrHPV test could reduce the need for follow up in these patients, bearing in mind that further studies are needed before specific recommendations can be made about the use of the hrHPV test in the follow-up of these women [12].

What do international guidelines recommend ?

The National Health System (NHS) guidelines in the United Kingdom (UK) regarding follow-up on hysterectomised women due to CIN2+ are based on expert opinions. These are summarised on Table 1. They base their recommendations on the fact that there is no clear evidence that colposcopy increases the detection of disease on follow-up [33].

They also address the role of HPV testing in the post-hysterectomy for CIN2+ scenario, stating that, as this is a small proportion of the total population at risk, it will be unlikely that guidance based on clinical trials will be available in the near future. However, along with vaginal cytology, they recommend parallel HPV testing, as this may facilitate the development of guidance on management of these women [33].

The following recommendations (Table 2) are fully explained in the Cancer Council Australia Cervical Cancer Screening Guidelines [5].

The US Preventive Services Task Force Recommendation Statement on cervical cancer screening and the ACOG are scant regarding vaginal vault hrHPV testing on women hysterectomised due to CIN2+. They only state that the role of HPV testing in this population has not yet been clarified, but do not specify if its use should be included or not on the follow-up of this specific group of women [4, 19]. The recommendations regarding the follow-up of hysterectomised women due to CIN2+ are summarised in Table 3 [4, 19].

Due to the scarce results on literature regarding vaginal cancer screening on which to base recommendations, some expert authors recommend adopting some recommendations from cervical cancer prevention guidelines when managing abnormal vaginal screening tests. The most important adaptation considers hrHPV testing: although it is not FDA-approved for vaginal specimens, its NPV is very high, and therefore reassuring that there is low risk of vaginal cancer [9].

Experts favour a conservative approach to management of abnormal vaginal tests in women with an history of CIN2+ who have completed the recommended surveillance after treatment and have initiated the late follow-up period (after five years post-treatment). This tactic is justified by the low PPV estimates for both vaginal cytology and hrHPV testing and the rarity of vaginal cancer, even in high-risk groups such as these women [34, 35]. Based on the fact that

Table 3. *Recommendations on follow-up of hysterectomised women due to CIN2+ by the US Preventive Services Task Force and ACOG.*

Premalignant or malignant lesion which motivated hysterectomy	Follow-up
Total hysterectomy for treatment of CIN2+ and adenocarcinoma in situ	Continue screening for 20 years after the last abnormal test result, even if it extends screening beyond age 65 years

Table 4. *Suggested follow-up algorithm for hysterectomised women due to CIN2+ on late follow-up period, based on expert opinions.*

Cytology/hrHPV testing results	Recommendations	Alternatives	Follow-up
ASC-US	1) Deferral of vaginal colposcopy	1) Immediate vaginal colposcopy if HPV16/18 positive	1) Negative/negative co-testing à routine screening until completion of 20 years
LSIL	2) Repeat vaginal co-testing in one year	2) Observation for up to two years: If HPV16/18 positive/negative cytology or HPV16/18 negative/ASC-US or LSIL	
	3) If persistently abnormal or hrHPV positive à vaginal colposcopy	3) If HPV testing is not available, repeat cytology one year later: if ≥ ASCUS à colposcopy	
HSIL Atypic glandular cells (AGC) ASC-H	1) Timely vaginal colposcopy	-	1) Negative vaginal colposcopy à repeat vaginal cytology and colposcopy in 6–12 months
Positive hrHPV test and negative cytology	1) Repeat cytology or co-testing in one year	-	-
	2) Any abnormalities after one year à vaginal colposcopy		

most recurrences occur within the first two to three years post-treatment, and that risk diminishes substantially after repetitive negative screening tests, these women can be managed similarly to low-risk women once all early follow-up surveillance tests are negative [9, 36].

An expert panel review on this topic suggested a follow-up algorithm for this specific population, that is summarised in Table 4 [9, 37].

Most guidelines do not specify the interval for surveillance in the late follow-up period. This group of experts proposes that women with negative/negative co-testing undergo surveillance tests at three-year intervals [38]. Symptomatic women with abnormal vaginal cytology, especially bleeding, or with visible vaginal lesions are not included in these recommendations [9].

Conclusions

Although the risk of vaginal recurrence is low, women with a history of hysterectomy for CIN2+ are a risk group for this pathology, and have a very prolonged follow-up

period after surgical treatment [12]. The present research on the literature on hrHPV vaginal screening test has defined areas of uncertainty. Further research is needed, not only through retrospective and cohort studies, but also by exploring institutional or administrative databases for outcomes after an abnormal vaginal cytology or hrHPV test, and after a diagnosis of VaIN [9]. High risk HPV vaginal testing may be helpful in detecting central recurrence at its early stage and allow more conservative types of surgery [24]. Research on this topic may provide the future possibility that hysterectomised women due to CIN2+ may be discharged after test of cure following only one negative co-test, or a single HPV-only test [5].

Conflict of Interest

The authors declare no competing interests.

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