OPEN

Human papillomavirus Posttreatment Clearance Time in Cervical Intraepithelial Neoplasia and Invasive Cervical Cancer

Guligeina Abudurexiti, MSc, Gulixian Tuerxun, PhD, Guzhalinuer Abulizi, PhD, Patiman Mijiti, MD, Kailibinuer Aierken, PhD, Anaerguli Maimaiti, MSc, and Hua Li, MSc

Objective: The aim of the study was to determine an appropriate follow-up schedule for human papillomavirus (HPV) detection by evaluating the clearance time of HPV after treatment.

Materials and Methods: A retrospective study was conducted on 97 high-grade squamous intraepithelial lesion (HSIL) (cervical intraepithelial neoplasia 2–3) patients and 437 early invasive cervical cancer (CC) (stages Ia–IIa) patients who received radical surgery at the Affiliated Tumor Hospital of Xinjiang Medical University. Patient medical information, including personal information, pathological diagnosis, HPV infection status, and therapeutic methods, was obtained through the hospital's historical medical records management system. The clearance time of HPV was determined using Kaplan-Meier method analysis, and clearance time of HPV among different age groups, different grades, and different clinical stages were compared using the log-rank test.

Results: The median clearance time of all patients was 10.4 months. The median clearance time was longer in HSIL patients than in early invasive CC patients ($p < .05$). No statistical significance was found among different HSIL grades, CC stages, or patient age groups ($P > 0.05$).

Conclusions: Delaying first posttreatment follow-up to 9 months in patients at high risk of noncompliance could potentially reduce burden of cost and repeated clinical visits. This follow-up approach could be consistently applied to all women regardless of age, severity, and extent of disease.

Key Words: cervical cancer, cervical intraepithelial neoplasia, human papilloma virus infection, clearance time, post treatment

(*J Low Genit Tract Dis* 2020;24: 34–37)

Cervical cancer is the second most common malignancy worldwide and is responsible for 280,000 deaths annually.[1] High-risk human papillomavirus (HPV) was found to be associated with cervical cancer (CC);[2] later, the diagnosis, treatment, and follow-up study of CC have been focused on HPV infection.[3] Medical treatments can treat cervical lesions caused by HPV infection and can also help the body to clear the virus. The loop electrosurgical excision procedure and the cervical cold-knife conization are the most common surgical procedures for high-grade squamous intraepithelial lesion (HSIL), whereas radical hysterectomy plus pelvic lymph node dissection is the classic surgery for early invasive CC. Radiotherapy and chemotherapy are primary treatments for middle- and late-stage invasive CC. It is shown that the risk of invasive CC for women who had received prior cervical lesion excisions was 10 times greater than that for women without any cervical lesion history.[4] Although symptoms and signs of CC may disappear after treatment, the disease recurs in some patients. Treatment is difficult for recurrent CC, and the prognosis is poor. Most patients will die within 2 years after recurrence, and the 5-year survival rate is approximately 10%.[5–7]

It has also been reported that persistent HPV infection after treatment is the key factor for relapse of cervical intraepithelial neoplasia (CIN) and CC. Therefore, it is crucial to evaluate HPV infection status in the follow-up period.[8,9] According to the Society of Gynecologic Oncology guideline, the components of posttreatment surveillance include physical examination, cytology, and HPV testing. Physical examinations are simple and inexpensive. However, microscopic lesions cannot be found only by physical examination. Cytology is widely used for posttreatment surveillance in clinic.[10] However, the accuracy of the cytology is closely related to sampling site. Human papillomavirus testing has high specificity and sensitivity and is reported to be effective in monitoring for CC recurrence.[11,12] The National Comprehensive Cancer Network guidelines recommend a follow-up strategy of every 3 to 6 month in the first 2 years for cervical lesions after therapy; however, which detection methods should be adopted, including HPV testing and cytology, is not specified. The rationale for HPV DNA testing in the follow-up of patients[13] relies primarily on its high negative predictive value, which could enormously reduce the burden of follow-up visits.

On average, 900 cases of CC and 350 cases of CIN are treated at the Affiliated Tumor Hospital of Xinjiang Medical University every year, who should be monitored for posttreatment recurrence. Therefore, in this study, we aimed to establish a reasonable follow-up management strategy for these patients.

MATERIALS AND METHODS

This was a retrospective study. Human papillomavirus–infected patients with HSIL (CIN 2–3) and early invasive CC (stages I–II (IIa) squamous cell cervical carcinoma) treated at the Affiliated Tumor Hospital of Xinjiang Medical University between 2012 and 2013 were recruited for the study. A total of 696 HSIL and 1904 early invasive CC patients were treated during that period. Finally, a total of 534 patients (97 HSIL and 437 early invasive CC) with complete available medical information were enrolled. The eligibility criteria were as follows: positive preoperative HPV DNA test results when HSIL or early invasive CC was first diagnosed; treated by electrosurgical excisional procedure; histologically confirmed diagnosis of HSIL and early invasive CC; and no recurrence of HSIL or early invasive CC during follow-up. Cytology and HPV testing are performed during follow-up after treatment. In some patients, although the cytology result is negative, HPV testing result is positive.

The HC-2 detection method was used before treatment and at every posttreatment follow-up visit. Each patient was diagnosed

5th Department of Gynecology, Affiliated Tumor Hospital of Xinjiang Medical University, Xinjiang, China

Reprint requests to: Guzhalinuer Abulizi, PhD, 5th Department of Gynecology, Affiliated Tumor Hospital of Xinjiang Medical University, No. 789, Suzhou East St, Urumqi 830054, Xinjiang Uyghur Autonomous Region, China 830054. E-mail: gzlnr@qq.com
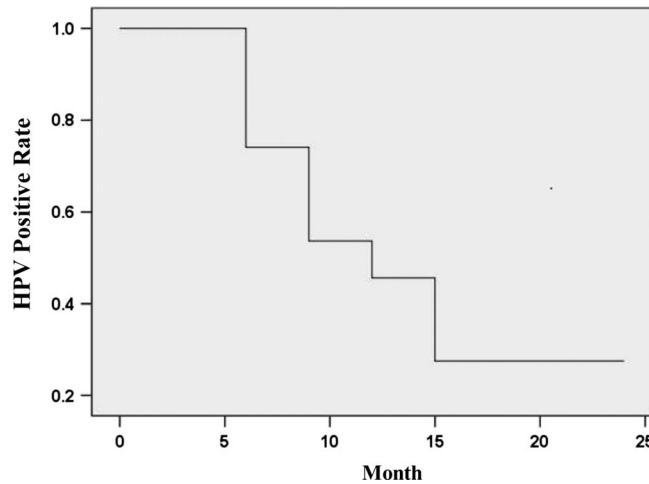
FIGURE 1. Analysis of median human papilloma virus clearance time.

based on pathological results of a cervical biopsy. Clinical stages for invasive CC patients were determined by 2 chief physicians with extensive experience in gynecological oncology. Standard treatments, including cervical conization, radical hysterectomy plus pelvic lymph node dissection, chemotherapy, and radiotherapy, were performed according to patients' diagnoses, and all therapeutic methods complied with the National Comprehensive Cancer Network guidelines. Follow-up procedures were scheduled at 3, 6, 9, 12, 18, and 24 months after treatment. All patients were examined by HC-2 and Pap smears; in the case of abnormal results, colposcopy was performed. Patients' medical information, including personal information, pathological diagnosis, HPV infection status, and therapeutic strategies, was obtained through the hospital's medical record management system. The final follow-up visits of patients were completed by December 2015. Written informed consent was obtained from each study participant before the study. The ethical committee of the Affiliated Tumor Hospital of Xinjiang Medical University approved the study.

Viral clearance was defined as a viral load of less than 1, as detected by the HC-2 method, without conversion to positive status through the remaining follow-up visits. The clearance time of HPV was determined using the Kaplan-Meier method (StataCorp, 2007; StataCorp. Survival analysis and epidemiological tables. Reference manual. Release 10. College Station, TX: Stata Press; 2007). Clearance time of HPV among different age groups, different grades, and different clinical stages were compared using the log-rank test. The significance level was determined as α level of 0.05.

Role of Funding Source

RESULTS

The study population was composed of 97 HSIL patients and 437 early invasive CC patients. Among these HSIL patients, the numbers of CIN 2 and CIN 3 patients were 20 and 77, respectively, whereas the numbers of stage I and II (IIa) CC patients were 147 and 290, respectively.

The 3-, 6-, 9-, 12-, 18-, and 24-month HPV clearance rates of all HSIL and early invasive CC after treatment were 25.84% (138/534), 46.25% (247/534), 54.31% (290/534), 72.47% (387/534), 82.95% (443/534), and 91.95% (491/534). A total of 147, 91, and 43 patients had persistent HPV infection at 12, 18, and 24 months, respectively. All these patients were tested by cytology. Biopsy under colposcopy was performed in cases of atypical squamous cells with undetermined significance. All patients were pathologically normal. The clearance rate of HPV increased along with the
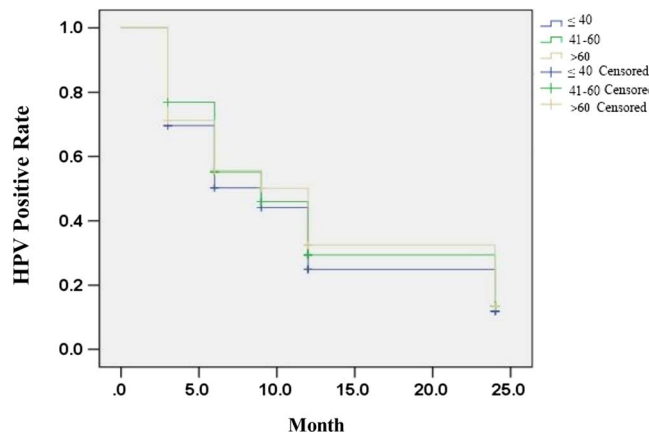

FIGURE 2. Analysis of median human papilloma virus clearance time among different age groups of patients.
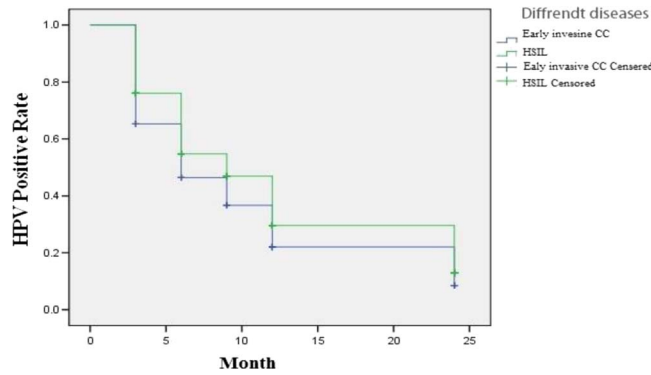
FIGURE 3. Analysis of median human papilloma virus clearance time among different disease types of patients.

length of follow-up. The median clearance time was 10.4 months (see Figure 1).

The youngest patient in the study was 23 years old, whereas the oldest one was 78 years old. When different age groups of patients were analyzed, the median clearance time at ages 40 years or younger, 41 to 60, and older than 60 were 9 months (95% CI = 6.91–11.09 months), 9 months (95% CI = 7.74–10.27 months), and 12 months (95% CI = 9.21–14.79 months), respectively. No statistically significant difference was found among different age groups ($p > .05$) (see Figure 2).

The median HPV clearance times of HSIL and early invasive CC were 9 months (95% CI = 7.89–10.11 months) and 6 months (95% CI = 4.28–7.72 months), respectively. The clearance time of HSIL was longer than that of early invasive CC ($p < .05$) (see Figure 3). The median clearance times of CIN 2 and CIN 3 were 12 months (95% CI = 8.50–15.50 months) and 6 months (95% CI = 4.24–7.76 months), respectively. The median clearance times of CC stages I and II (IIa) were 9 months (95% CI = 7.13–10.87 months) and 9 months (95% CI = 7.62–10.38 months), respectively. No statistical difference was found among different CIN grades ($p > .05$, $p = .31$) (see Figure 4) or different CC stages ($p > .05$, $p = .93$) (see Figure 5).

DISCUSSION

There is HPV DNA in almost all CC specimens. Human papillomavirus testing is, therefore, important for screening and monitoring of patients after treatment for HSIL and early invasive CC. In addition, cytology and virology detection methods have been widely used in gynecological oncology, thus enabling cervical-lesion patients to receive timely and accurate treatment.[14]

Clinical research and epidemiological data have demonstrated that most HPV infections are temporary and can be cleared naturally. Different median time to viral clearance have been reported (e.g., 7 and 19 months)[15] in the literature based on different study populations, different detection methods, and different follow-up methods. During follow-ups, clinical physicians often find that the virus clearance needs a certain amount of time in most HSIL and early invasive CC patients after treatment. Surgery, radiotherapy, and chemotherapy cannot clear all HPV and clearing the remnants of HPV relies on the immune function of the body. Therefore, the specific HPV clearance times for HSIL and early invasive CC are not fully clear. In this study, the 3-, 6-, 9-, 12-, 18-, and 24-month HPV clearance times of HSIL and early invasive CC after treatment were 25.84%, 46.25%, 54.31%, 72.47%, 82.95%, and 91.95%, respectively, and the median time of HPV clearance was 10.4 months. Nearly half of the patients were HPV positive with negative ThinPrep cytology or cervical biopsy at first and second visits, indicating that HPV testing for follow-up after treatment could be started at 6 to 9 months. This could enormously reduce the burden of follow-up visits, and thus, the physicians' efforts could concentrate on HPV-positive patients. It is also reported that the sensitivity and specificity of HPV testing are higher than those of physical examination and cytology testing.[16] Thus, standard HPV testing in follow-up of patients treated for HSIL or early invasive CC is an optional strategy for detecting HPV clearance and for early detection of recurrence of disease.

One prior report has pointed out that HPV clearance was associated with age.[17] However, Gulibanu et al[18] found that HPV clearance and age were unrelated in a recent study of Chinese women. In our study, patients' ages were not related to their clearance times for both HSIL and early invasive CC, which is consistent with the findings of Gulibanu et al.[18] However, the relationship between age and HPV clearance time needs to be further studied with a larger sample size.

It can take decades for cervical HPV infection to develop into HSIL and progress into early invasive CC. Therefore, early detection and early treatment for patients with cervical lesions will not only improve their quality of life but also reduce the
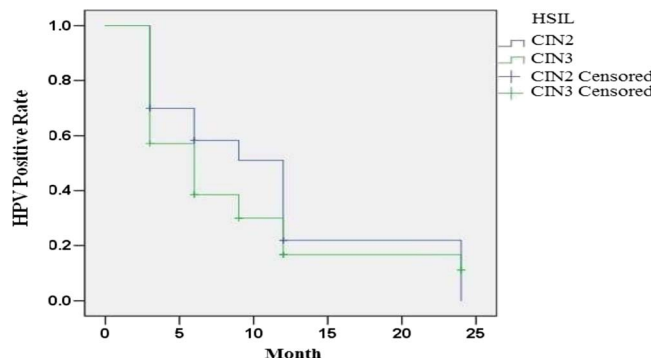

FIGURE 4. Analysis of median human papilloma virus clearance time among different cervical intraepithelial neoplasia grades of patients.
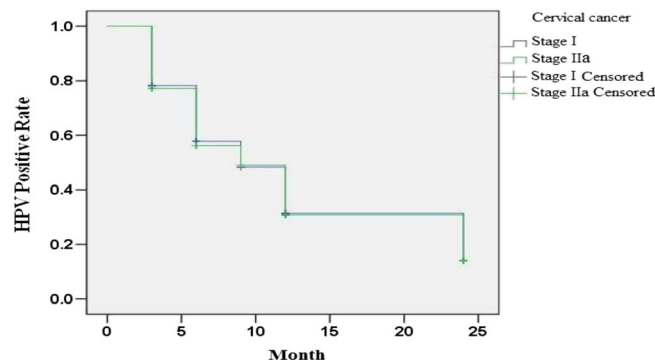
FIGURE 5. Analysis of median human papilloma virus clearance time among different cervical cancer stages of patients.

morbidity and mortality of CC. One study in China reported[19] that the median HPV clearance time of early invasive CC patients was shorter than that of HSIL patients. We found similar results in this study. This may be because the range of radical CC surgery is large enough for effective and rapid HPV clearance and can also remove the residual cancerous tissue, thereby preventing recurrence as much as possible. However, no statistically significant difference in HPV clearance time was found among different grades of HSIL and different stages of early invasive CC in the current study.

CONCLUSIONS

Based on our findings, the median clearance time of HPV was 10.4 months, so delaying first posttreatment follow-up time to 9 months in patients at high risk of noncompliance could potentially reduce burden of cost and repeated clinical visits without significantly compromising patient's safety. This follow-up approach could be consistently applied to all women regardless of age, severity, and extent of disease.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.

2. zur Hausen H. Papillomavirus infections-a major cause of human cancers. *Biochim Biophys Acta* 1996;1288:F55–78.

3. Kashyap V, Hedau S, Bhambhani S. Defining the validity of classical and non-classical cellular changes indicative of low-grade squamous intraepithelial lesion encompassing human papillomavirus infection in relation to human papillomavirus deoxyribonucleic acid testing. *J Cytol* 2011;28:159–64.

4. Chatterjee R, Mandal B, Bandhopadhyay S. Detection of HPV DNA in cervical carcinomas after treatment in India. *Int J Hum Genet* 2005;5:27–31.

5. Ikushima H, Osaki K, Furutani S, et al. Chemoradiation therapy for cervical cancer: toxicity of concurrent weekly cisplatin. *Radiat Med* 2006;24:115–21.

6. Uno T, Mitsuhashi A, Isobe K, et al. Concurrent daily cisplatin and extended-field radiation therapy for carcinoma of the cervix. *Int J Gynecol Cancer* 2008;18:80–4.

7. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008;26:5802–12.

8. Kjaer SK, van den Brule AJ, Paull G, et al. Type specific persistence of high risk human papilloma virus as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow up study. *BMJ* 2002;325:572.

9. Moberg M, Gustavsson I, Wilander E, et al. High viral loads of human papilloma virus predict risk of invasive cervical carcinoma. *Br J Cancer* 2005;92:891–4.

10. Elit L, Kennedy EB, Fyles A, et al. Follow-up for cervical cancer: a program in evidence-based care systematic review and clinical practice guideline update. *Curr Oncol* 2016;23:109–18.

11. Song D, Kong WM, Zhang TQ, et al. The negative conversion of high-risk human papillomavirus and its performance in surveillance of cervical cancer after treatment: a retrospective study. *Arch Gynecol Obstet* 2017;295:197–203.

12. Hillemanns P. The paradigm shift in cervical cancer screening in Germany. *Arch Gynecol Obstet* 2016;293:3–4.

13. Costa S, Sideri M, Negri G, et al. The predictive value of human papillomavirus testing for the outcome of patients conservatively treated for stage IA squamous cell cervical carcinoma. *J Clin Virol* 2015;70:53–7.

14. Kjellberg L, Wadell G, Bergman F, et al. Regular disappearance of the human papillomavirus genome after conization of cervical dysplasia by carbon dioxide laser. *Am J Obstet Gynecol* 2000;183:1238–42.

15. Nobbenhuis MA, Helmerhorst TJ, van den Brule AJ, et al. High risk human papillomavirus clearance in pregnant women: trends for lower clearance during pregnancy with a catch-up postpartum. *Br J Cancer* 2002;87:75–80.

16. Costa S, Venturoli S, Origoni M, et al. Performance of HPV DNA testing in the follow-up after treatment of high-grade cervical lesions, adenocarcinoma in situ (AIS) and microinvasive carcinoma. *Ecancermedicalscience* 2015;9:528.

17. Dalstein V, Riethmuller D, Pretet JL, et al. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. *Int J Cancer* 2003;106:396–403.

18. Gulibanu M, Mayinuer N, et al. Related factors of effects on HPV regression after treatment of cervical intraepithelial neoplasia among Han and Uyghur women [in Chinese]. *Xinjiang Med J* 2013;43:15–9.

19. Li Yuanyuan. A Correlation Study of HR-HPV and Cervical Cancer and Precancerous Lesions in the Occurrence and Prognosis [dissertation, in Chinese]. Shihezi: Shihezi University. 2013:1–29.