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Residual disease and presence of human papillomavirus after conization

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SUMMARY: **Residual disease and presence of human papillomavirus after conization.**

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The development of invasive carcinoma following treatment by loop excision biopsy is considered a failure of treatment

In this study we evaluate human papillomavirus deoxyribonucleic acid testing after conization in predicting residual disease.

In 56 of 58 patients (96.6%), HPV DNAs were detected in their primary cervical lesions prior to conization.

Up to August 2000, all of the 58 patients have been followed with a mean follow-up period of 31.8 months (range: 12 to 73 months).

After treatment, HPV DNA was persistently detected in 11 (19.6%) but negative in 45 (80.4%) of 56 HPV DNA-positive patients.

Five of 11 persistently HPV DNA-positive patients (45.5%) developed CIN recurrence, while none of 45 persistently HPV DNA-negative patients did.

This study confirms an exellent sensitivity and negative predictive value of HPV-DNA testing after conization in predicting residual cervical neoplasia.

RIASSUNTO: **Associazione tra presenza HPV e malattia residua dopo conizzazione.**

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La presenza di malattia residua dopo conizzazione è considerata un fallimento del trattamento.

In questo studio il test per la ricerca dell'HPV dopo conizzazione è stato utilizzato per predire la presenza di malattia residua.

In 56 delle 58 donne valutate (96,6%) è stata riscontrata la presenza di HPV nella lesione primaria, prima della conizzazione.

Fino all'agosto 2000, tutte le 58 donne sono state sottoposte ad un periodo di follow-up di 31,8 mesi (il range variava dai 12 ai 73 mesi).

Dopo il trattamento, la ricerca dell'HPV-DNA è risultata positiva in 11 casi (19,6%) e negativa in 45 delle 56 pazienti HPV-DNA positive.

In 5 delle 11 pazienti (45,5%) positive per l'HPV-DNA si è sviluppata una CIN, mentre in nessuna delle 45 pazienti risultate negative per l'HPV-DNA è stata riscontrata una ricorrenza di malattia.

Questo studio conferma l'alta sensibilità e il valore predittivo negativo dell'HPV-DNA test dopo conizzazione per predire la malattia residua.

KEY WORDS: Conization - HPV-DNA testing - Residual disease.
Test per la ricerca all'HPV-DNA - Malattia residua.

Introduction

Loop excision biopsy, also known as LLETZ (large loop excision of the transformation zone), is the most common and popular method of treatment of cervical intraepithelial neoplasia (CIN). Loop biopsies are performed for both diagnostic and therapeutic purposes. The histological evaluation of the loop excision biopsy specimen takes into account the grade of CIN, the status of the margins of resection, the presence or absence of CIN in endocervical crypts, the presence or absence of invasion and cervical glandular intraepithelial neoplasia, and any other associated pathology. The factors that have been associated with the failure of treatment or recurrence of CIN include the presence of CIN at ectocervical and endocervical margins of resection, involvement of endocervical glands, large CIN lesions, depth of the loop, high grade of CIN, and the age of the patient. The development of invasive carcinoma following treatment by loop excision biopsy is considered a failure of treatment. No biological markers or technologies useful to predict the natural history of an individual CIN III are known. The probability of progression is considered greater with the persistence of high-risk human papillomavirus (HPV) infection and age. In this study we evaluate the human papillomavirus deoxyribonucleic acid testing after conization with reference to the prediction of residual disease.

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Materials and methods

The present study deals with 58 patients who were

tested for HPV DNA in the pre-treatment cervical lesions, out of the 74 who referred with CIN 3. After standard therapeutic conization, patients were followed prospectively at the outpatient clinic. Our follow-up protocol was to follow patients without therapeutic intervention as long as they developed no recurrence or recurrence of CIN 1 or 2; while patients who experienced recurrence of CIN 3 were recommended reconization or hysterectomy. The polymerase chain reaction for detecting HPV DNA was performed using fresh cell samples from the cervix.

Results

In 56 out of the 58 patients (96.6%), HPV DNAs were detected in their primary cervical lesions prior to conization. With regard to the distribution of HPV types, HPV type 16 family (types 16, 31, and 35) was identified in 28 cases (50.0%), type 18 family (types 18, 33 and 58) in 15 (26.8%), and type X in 18 (32.1%). Up to August 2000, all the 58 patients were followed-up for a mean period of 31.8 months (range: 12 to 73 months). After treatment, HPV DNA was persistently detected in 11 (19.6%) of the 56 HPV DNA-positive patients, but 45 (80.4%) of them were found HPV DNA- negative. HPV DNA was not detected in both HPV DNA-negative patients. Five of the 11 persistently HPV DNA-positive patients (45.5%) developed CIN recurrence, while none of the 45 persistently HPV DNA-negative patients did. Thus, there was a significant difference between the recurrence rates of these two groups ($P < 0.0001$). Both patients who were initially HPV DNA-negative developed no recurrence. Accordingly, the overall recurrence following conservative treatment for CIN 3 was 5 patients out of 58 (8.6%).

Discussion and conclusions

Persistent HPV infection appears to be a clear risk factor for persistent cervical intraepithelial neoplasia (CIN II) and type-specific persistence of high-risk HPV infection is a good predictor of the possibility of developing high-grade lesions. HPV seems to be a stronger predictor of persistent cervical abnormalities in women over 35. Certain types of HPV and persistent high loads of viral infection may be associated with increased risks of cervical neoplasia, but whether this justifies HPV DNA screening is still open to debate. HPV remains detectable longer than cervical cytologic abnormalities, suggesting that HPV DNA testing may be a more sensitive test for HPV infection and that there may be a role for HPV- DNA testing in women with ambiguous cytology results. Women treated for CIN2 or CIN3 remain at increased risk of cervical cancer for at least 8 years in comparison with the general population. Generally, cytology and/or colposcopy have been used for post-treatment surveillance. HPV testing deserves investigation as another possible strategy to monitor the efficacy of the treatment. Several small studies have shown that HPV DNA clearance is associated with low risk of subsequent CIN after treatment, and persistent HPV positivity predicts increased risk of treatment failure. However, the possibility of vaginal recolonization with HPV or a new HPV infection with another HPV type must be considered. This study confirms the excellent sensitivity and negative predictive value of HPV-DNA testing after conization as far as the prediction of residual cervical neoplasia is concerned. Patients with persistent HPV infection after conization for CIN 3 should be closely followed because they are at increased risk of developing disease recurrence.

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