ACTA SCIENTIFIC CANCER BIOLOGY

Volume 3 Issue 8 August 2019

Review Article

Decision-to-Treat Outpatients for High Grade CIN at a Colposcopy Clinic in India

Priya Ganesh Kumar[1]*, Akshay Ganesh Kumar[2] and Dinesh Gupta

[1]*Sai Niwas Health Care for Women and Advanced Colposcopy Centre, Thane, Mumbai, India*

[2]*AIIMS, New Delhi, India*

[3]*Cure Health Diagnostics, East of Kailash, New Delhi, India*

***Corresponding Author:** Priya Ganesh Kumar, Sai Niwas Health Care for Women and Advanced Colposcopy Centre, Thane, Mumbai, India.

Received: July 09, 2019; **Published:** July 26, 2019

Abstract

Clinical detection of Human Papillomavirus DNA test has become a standard of diagnostic care and treatment for high grade cervical intraepithelial neoplastic (CIN2+) lesion at the outpatient clinics in India. A detection of HPV DNA has been well established to show an increased risk for cervical cancer development owing to its superior sensitivity and its negative precancer disease prediction. Most HPV infections remain asymptomatic, or self-limited that resolve within 12 to 24 months of primary infection. Therefore considering a much wider and longer prevalence of HPV among most sexually active women during their active age, a single round of HPV DNA testing does not establish persistence of viral infection, thereby dropping considerably on the test specificity. This strategy leads to multiple rounds of sequential testing by cytologic or histopathologic methods for correctly detecting high grade precancer for HPV positive women at the outpatient wards, posing clinical challenge as well as psychologic dilemma for patients. Often discordant colposcopy and/or histopathology findings thereby delay the surgical interventions at the outpatient clinics, particularly for relatively younger and/or symptomatic outpatients. The present study was undertaken to assess the sensitivity and specificity of HPV Onco Test® test among symptomatic outpatients. The Onco Test® assay for Human papillomavirus E6/E7 mRNA testing (Incell Dx, CA) is a flow cytometry based in situ hybridization test for the detection of HPV E6 and E7 mRNA in intact squamous cells.

Biomolecular diagnostics with m RNA E6/E7 could certainly provide a good concordance in high grade lesions. This test being more specific with high PPV becomes positive in the integrated HPV lesions, thereby giving clinicians a fair idea for treatment planning and further follow up.

Concurrent diagnostics methodology using colposcopy and m RNA provides a definitive answer in this grey zone of treatment and prognosis of precancerous lesions.

Keywords: High Grade; Clinic; CIN

Introduction

Lately, clinical detection of Human Papillomavirus (HPV) has become a standard of diagnostic care and treatment for high grade cervical intraepithelial neoplastic (CIN2+) lesion at the outpatient clinics in India. Detection of HPV DNA has been well established to show an increased risk for cervical cancer development [1] owing to its superior sensitivity and its high negative predictive value for precancer detection [3,4]. Most HPV infections remain asymptomatic, or self-limited that resolve within 12 to 24 months of primary infection. Therefore considering a much higher prevalence of HPV among most sexually active women and repeated re-infections post clearing of an existing one, a single round of HPV DNA testing does not establish persistence of viral infection, thereby dropping considerably on the test specificity [5,6]. Thus, strategies of screening

demand multiple rounds of sequential testing by cytologic or histopathologic methods for correctly detecting high grade precancer in HPV positive women in the outpatient setting, posing clinical challenge as well as psychologic dilemma for patients. Often discordant colposcopy and/or histopathology findings thereby delay interventions at the outpatient clinics, particularly for relatively younger and/or asymptomatic outpatients. In the largely private sector healthcare domain in India, strategies such as visual inspection with acetic acid (VIA) and followed by high sensitivity testing for oncogenic HPV types could potentially make prevention of cervical cancer more feasible than relying simply upon a single round of HPV DNA testing; both by improving sensitivity as compared to solely relying upon PAP/VIA and improving specificity as compared to a single round of HPV DNA testing. A clinically robust test with a higher positive disease prediction amongst symptomatic outpatients may further bring down the cost of the management of women with high grade precancer [6,7]. The present study was undertaken to assess the sensitivity and specificity of HPV OncoTect® test among symptomatic outpatients. The OncoTect® assay for Human papillomavirus E6/E7 mRNA testing (IncellDx, CA) is a flow cytometry based in situ hybridization test for the detection of HPV E6 and E7 mRNA in intact squamous cells. HPV OncoTect takes advantage of the fact that oncogenic genotypes of HPV overexpress E6 and E7 mRNA following integration of HPV into genomic DNA. The presence of high levels of HPV E6, E7 mRNA have been shown to indicate that these cells undergo molecular transformation during the high grade precancer development and are associated with increased histopathologic lesion severity [9-11], therefore the detection of E6/E7 mRNA may be of higher prognostic value and may improve the specificity and positive predictive value compared with HPV DNA testing in screening.

The molecular mechanism of HPV infection has been extensively studied over past two decades that involves viral oncogenes E6 and E7 expression that transform normal cells to acquire malignant potential, and be responsible to trigger cervical carcinogenesis in the cascading mechanism [6-8]. The nucleic acid assay based on oncogenic messenger RNA detection, namely HPV OncoTect (IncellDx, California, USA) offers high specificity for CIN2+ at routine clinical use and we determined its specificity in our clinical practice to guide our colposcopy and directed histopathology to arrive at a decision to treat the symptomatic patients.

Materials and Methods

A cohort of 250 sexually active women between 25 to 60 years of age, attending the gynecology OPD, were screened simultaneously with per speculum examination, HPV DNA by HC2® and HPV E6/E7 mRNA (or HPV OncoTect®) assay. All specimens were collected using the LiquiPrep® medium.

Women with HC2 and/or HPV OncoTect positive were subjected to colposcopy directed biopsy of cervix. Main outcome measure was to study pick up rate for correctly detecting any HR HPV positive cervical lesions above CIN1 to be able to offer a close clinical surveillance so that no disease is allowed to progress among symptomatic outpatients of the hospital.

Outpatients with symptomatic presentation of at least one of the major symptom, such as leucorrhoea, dyspareunia, post coital bleeding, postmenopausal bleeding, burning micturition, post-Werthims vault screening, vaginal wall screening in case of cervical growth were selected for the study. A liquid cytology (LBC) as method of primary screening was undertaken at VIA followed with colposcopic examination in all the cases and wherever required cervical punch biopsy was taken from the lesion for histopathology examinations. In cases where colposcopy revealed lesions by Swede score 5 or above, the specimen were triaged with mRNA. Immunohistochemistry (IHC)forp16^{ink4a} was performed in certain cases of High grade lesion. Due to financial constraints on patients, some patients with high grade lesions could not take mRNA test.

Results

Clinical Diagnosis	Nos	%
Total cases	250	
Normal	203	81%
CIN 1	35	14.0%
CIN 2	8	3.2%
CIN 3	4	1.6%
% High Grade CIN (CIN2+3)	12	4.8%

Table 1: Total cases June15-May16.

Colposcopy findings	Nos	%
Normal	157	62.8%
Chronic cervicitis	14	5.6%
Polyp + Cysts (Nebothian)	6	2.4%
Ectropion	16	6.4%
Flat Condyloma	3	1.2%
CIN 1	35	14.0%
CIN 2	12	4.8%
CIN 3	3	1.2%
VAIN	1	0.4%
Adenocarcinoma	1	0.4%
Squamous Carcinoma	1	0.4%
Vault CA	1	0.4%
	250	

Table 2

Concordance with HP	Concordance	%	Discordance	%
CIN 1	30	86%	6	17%
CIN 2	7	88%	4	50%
CIN 3	3	75%	1	25%

Table 3

PAP SMEAR	Concordance	%
Inflammatory	230	92.0%
ASC-H	5	2.0%
LSIL Koilocytic changes	12	4.8%
HSIL	3	1.2%

Table 4

E6E7 mRNA	25	% concordance HP
CIN1	1	3.3%
CIN1 (including VAIN)	2	6.7%
CIN2	4	57%
CIN3	3	100%
Negative	17	68%

Table 5

Distribution of cases according to symptoms

Major Symptoms	No. of Patients	% of Total Patients
White discharge with cases of dyspareunia, dysmenorrhea	148	59%
Menopausal white discharge with SUI (incidental findings)	12	5%
Recurrent UTI	15	6%
Abnormal bleeding (post- ore intra coital, post-menopausal)	29	11.8%
Menorrhagia, Irregular period	12	5%
Follow up CIN 1/2 cases opted for no treatment	03	1%
Post-treatment follow up (Electro-cautery, Cryotherapy, LEEP)	31	12.6%

Table 6

Discussion

Colposcopy being more observer specific remains an art backed by science. In today's evidence based practice, clients wants a very specific answer pertaining to disease diagnosis, prognosis, and treatment methodologies. The service providers have to give a clear cut guidelines as to when to intervene and treat. Till date before the era of biomolecular diagnostics, the clinician were largely dependent on colposcopy with guided biopsy along with cytology. As per analysis of the data, concordance with HP is 75-86%.

Cytology could detect 3 out of 12 cases with concordance of only 25% of high grade lesion, thus with very low sensitivity, 9 CIN 2/3 cases missed out.

Biomolecular diagnostics with m RNA E6/E7 could certainly provide a good concordance in high grade lesions -62% (8 out of 13 cases). This test being more specific with high PPV becomes positive in the integrated HPV lesions, thereby giving clinicians a fair idea for treatment planning and further follow up.

Few interesting case discussion on concurrent diagnostics

- 56yrs post menopausal bleeding could be confidentially advised for follow up without any surgical intervention of hysterectomy as her colposcopy and m RNA was negative.
- 58yrs old postmenopausal bleeding case of CIN 2 on colposcopy and HP, was m RNA positive, she opted for a simple hysterectomy. (she was advised LEEPS)

- 28yr old CIN 1 case with high m RNA was advised annual checkup with m RNA and Colposcopy examination to pick up progression of the disease at the earliest.
- 44yrs CIN 2 case with m RNA positive underwent LEEP therapy in two month.Her disease had progressed to CIN 3 as per her LEEP specimen HP within two months.
- 36yrs CIN2 case with m RNA negative underwent LEEP after 6 months, Her HP report of LEEP specimen was CIN 1.

Inference

Concurrent diagnostics methodology using colposcopy and m RNA provides a definitive answer in this grey zone of treatment and prognosis of precancerous lesions.

Acknowledgement

Dr Dinesh Gupta, Cure health Diagnostics, East of Kailash, New Delhi Dr Puneet Chandna., Precision Oncologist.

Bibliography

1. Bosch FX., *et al*. "The causal relation between human papillomavirus and cervical cancer". *Journal of Clinical Pathology* 55 (2002): 244-265.
2. Walboomers JM., *et al*. "Human papillomavirus is a necessary cause of invasive cervical cancer worldwide". *The Journal of pathology* 189 (1999): 12-19.
3. Boulet GAV., *et al*. "Human papillomavirus in cervical cancer screening: important role as biomarker". Cancer epidemiology, biomarkers and prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 17 (2008): 810-817.
4. Castle PE., *et al*. "Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study". *The Lancet Oncology* 12 (2011): 880-890.
5. Duensing S and Mu¨nger K. "Centrosome abnormalities, genomic instability and carcinogenic progression". *Biochimica et biophysica acta* 1471 (2001): M81-88.
6. Duensing S and Mu¨nger K. "The human papillomavirus type 16 E6 and E7 oncoproteins independently induce numerical and structural chromosome instability". *Cancer research* 62 (2002): 7075-7082.
7. Mu¨nger K., *et al*. "Biological activities and molecular targets of the human papillomavirus E7 oncoprotein". *Oncogene* 20 (2001): 7888-7898.
8. Mu¨nger K., *et al*. "Mechanisms of human papillomavirus-induced oncogenesis". *Journal of Virology* 78 (2004): 11451-11460.
9. Lie AK., *et al*. "DNA-versus RNA-based methods for human papillomavirus detection in cervical neoplasia". *Gynecologic Oncology* 97 (2005): 908-915.
10. Sotlar K., *et al*. "Detection of high-risk human papillomavirus E6 and E7 oncogene transcripts in cervical scrapes by nested RT-polymerase chain reaction". *Journal of Medical Virology* 74 (2004): 107-116.
11. Castle PE., *et al*. "A cross-sectional study of a prototype carcinogenic human papillomavirus E6/E7 messenger RNA assay for detection of cervical precancer and cancer". *Clinical Cancer Research* 13 (2007): 2599-2605.

Volume 3 Issue 8 August 2019