

ANAL CANCER SCREENING: TEST CHARACTERISTICS OF CYTOLOGY AND ONCOGENIC HPV TESTING FOR THE DETECTION OF ANAL DYSPLASIA



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ABSTRACT

Background: HIV-positive men remain at high risk for anal cancer despite the use of highly active antiretroviral therapy (HAART). We initiated an anal cancer screening study using anal Pap smears, human papillomavirus (HPV) detection and high resolution anoscopy (HRA) with directed anal biopsy. The aim of this study was to determine the test characteristics of the anal Pap smear and oncogenic HPV testing for the detection of histologic high-grade squamous intra-epithelial lesions (HSIL).

Methods: Subjects were HIV-positive men with a history of anal receptive intercourse. Cytology specimens were obtained by vigorously rotating Dacron swabs in the anal canal. Papanicolaou smears were prepared using a liquid-based method (ThinPrep™). Presence or absence of oncogenic HPV was determined using the Hybrid Capture assay. The Pap smears and biopsies were independently assessed by 4 blinded pathologists using the Bethesda criteria. Results were analyzed using these consensus diagnoses. The reference standard was the consensus diagnosis of histologic HSIL.

Results: Results are presented on 246 patients (median age=45, median CD4=400, median viral load <50, 89% on HAART). Pap smears were abnormal in 73% of subjects: HSIL in 7%, low-grade changes (LSIL) in 50%, and ASCUS in 16%. Anal biopsies were abnormal in 71%: HSIL in 28% and LSIL in 43%. The sensitivity (Sn) of any abnormality on the Pap for detecting histologic HSIL was 84% and the specificity (Sp) was 32%. Negative predictive value (NPV) was 84%. Positive predictive value (PPV) was 33% and the Pap smears missed detecting only 11/70 (16%) histologic HSIL lesions. HSIL on Pap smear testing was not strongly predictive of histologic HSIL. Of 18 patients with HSIL on Pap smear testing, only 12 (67%) had histologic HSIL. Sn was 17% and Sp was 97%. Oncogenic HPV was found in 86% of subjects. The presence of HPV had a Sn of 89%, Sp of 19%, NPV of 97%, PPV of 28%. Detection of HPV missed only 1/67 (1.5%) of HSIL lesions.

Conclusions: High rates of dysplasia have been detected during anal cancer screening. Any abnormality on the Pap smear was sensitive but not specific in detecting HSIL. Detection of oncogenic HPV had similar performance characteristics to the Pap

INTRODUCTION

ANAL CANCER

- Human papillomavirus-associated cancer
- Similar to cervical cancer, it is likely preceded by progressive dysplastic changes: LSIL (or AIN 1) to HSIL (AIN 2/3) to Cancer

RATES

- Incidence in general population: <1 per 100,000 (one-tenth the current rate of cervical cancer in U.S.)
- HIV-negative gay men : 35/100,000
- HIV-positive gay men : ~70/100,000
- May not be decreasing despite effective antiretroviral therapy
- Second most common cancer seen in our HIV clinic

THE "TRACE" ANAL CANCER SCREENING STUDY

- The Toronto Anal Cancer Evaluation Study (TRACE) was initiated in July 2002: it is a screening study for HIV-positive men with a history of anal-receptive intercourse
- All subjects have anal cytology (Pap smears), HPV testing, and high resolution anoscopy with directed biopsy
- 310 HIV+ men have been screened to date
- Results on the first 246 subjects are reported here

PRIMARY STUDY OUTCOME

To determine the test performance characteristics of cytology and HPV testing in identifying immediate anal cancer precursors

METHODS

GENERAL

- The anal Pap smear was obtained by rubbing a Dacron swab in the anal canal and was prepared using a liquid-based method (ThinPrep)
- HPV was detected by Hybrid Capture from the supernatant of ThinPrep solution
- HPV type-specific real-time PCR assays were performed in the LightCycler™
- High resolution anoscopy (colposcopy) with digital capture of images
- Anal biopsies were taken from areas suspected to be dysplastic based on the appearance during high resolution anoscopy (HRA) and after application of dilute vinegar and Lugol's iodine to the mucosa
- HSIL lesions were treated by ablative therapy and those patients are followed

PATHOLOGY

- Anal Pap smears and anal biopsy specimens were each coded with random generated numbers so the cytology and histology specimens could not be linked to each other by the pathologists
- The Pap smears were screened by cytopathology technologists who gave a preliminary diagnosis and highlighted abnormal areas
- Two to four study pathologists reviewed all specimens independently and they reached a consensus diagnosis on each of these specimens
- The reference standard was the consensus diagnosis of histologic HSIL.
- Diagnostic cytology categories were limited to: Normal, ASCUS, LSIL, HSIL, Cancer or Inadequate specimen for assessment
- Diagnostic histology categories were limited to: Normal, LSIL (AIN 1), HSIL (AIN 2/3), Cancer or Inadequate specimen for assessment

RESULTS

- 246 subjects
- median age=45, median CD4=400, median viral load <50
- 89% on HAART
- HPV
- Any HPV was found in 97% of subjects
- Multiple HPV types in 92%
- High-risk (oncogenic) types of HPV were found in 86% of subjects

Commonest HPV types:

- HPV 16 (39%)
- HPV 18 (24%)
- HPV 31 (15%)
- HPV 53 (26%)
- HPV 52 (23%)

RESULTS

ANAL CYTOLOGY (PAP SMEARS) (Abnormal in 73% of Subjects)

- ASCUS (16%)
- Low-grade changes (LSIL) (50%)
- High-grade changes (HSIL) (7%)

BIOPSY (Abnormal in 71% of Subjects)

- Low-grade changes (LSIL) – (43%)
- High-grade changes (HSIL) – (28%)

HIGH RESOLUTION ANOSCOPY (Abnormal in 78%)

- Warts - 56 % LSIL - 46%
- HSIL - 26% Cancer - 1%

RESULTS

HISTOPATHOLOGY

	NORMAL	LSIL	HSIL	TOTAL
NORMAL	37	19	11	67
ASCUS/LSIL	32	82	47	161
HSIL	2	4	12	18
TOTAL	71	105	70	246

HISTOPATHOLOGY

	NORMAL	LSIL	HSIL	TOTAL
PRESENT	47	88	66	201
ABSENT	22	10	1	33
TOTAL	69	98	67	234

CYTOLOGY

ONCOGENIC HPV

RESULTS

TEST CHARACTERISTICS

ANAL CYTOLOGY (any abnormality)

- The sensitivity (Sn) of any abnormality on cytology for detecting histologic HSIL was 84% and the specificity (Sp) was 32%
- Negative predictive value (NPV) = 84%, Positive predictive value (PPV) = 33%
- Cytology missed only 11/70 (16%) histologic HSIL lesions

ANAL CYTOLOGY (HSIL)

- HSIL on cytology was not strongly predictive of histologic HSIL. Of 18 patients with HSIL on cytology, only 12 (67%) had histologic HSIL; Sn was 17% and Sp was 97%.

ONCOGENIC HPV DETECTION

- The presence of HPV had a Sn of 99%, Sp of 19% for HSIL detection
- NPV = 97%, PPV = 28%.
- Detection of HPV missed only 1/67 (1.5%) of HSIL lesions.

SUMMARY

1. The TRACE anal cancer screening study has been initiated for HIV+ men with a history of anal receptive intercourse
2. Abnormalities were found in 73% by Pap smear, 71% by histology and in 78% by anoscopy
3. High grade pre-cancerous changes were found in 31% of subjects by either Pap smear or histology
4. High risk (oncogenic) HPV types were found in 89%
5. Anal cytology was sensitive but not specific for detecting histologic HSIL (AIN 2/3)
6. HPV detection was also sensitive but not specific for detecting histologic HSIL (AIN 2/3)
7. Negative HPV testing or normal cytology were helpful in excluding histologic HSIL (AIN 2/3)
8. High-resolution anoscopy may be required to adequately detect high-grade dysplasia (HSIL or AIN 2/3)