HPV testing in cervicovaginal cytology

Dina R. Mody, MD
ASC-US triage. High-risk HPV typing has more or less become the standard for atypical squamous cells of undetermined significance, or ASC-US triage. Thanks to the ALTs trial and American Society for Colposcopy and Cervical Pathology guidelines, 1 some health care providers and insurance carriers now offer HPV testing in conjunction with a pap smear. Although this has been available for more than a year, many payers do not cover this test and many providers do not offer it. With the publication of the interim guidance document 2 and the HART study, 3 some of the issues related to managing women with disparity between high-risk HPV typing and an abnormal Pap test may be clarified. The interim guidance document offers the following recommendations:

- Age to initiate: 30 years or more.
- Age to discontinue: 65 years as per U.S. Preventive Service recommendations for cervicovaginal screening or age 70 as per American Cancer Society recommendations.
- Who should not receive HPV DNA testing in screening mode? Women under 30, immunocompromised patients, and patients who have had a total hysterectomy for benign gynecologic disease.
- A combination of negative high-risk HPV typing and a negative cytology should result in longer screening intervals, that is, three years.
- For cytology-negative, HPV-positive patients, repeat both in six to 12 months.

¢ For HPV-negative but abnormal cytology, follow up as per management for abnormal cytology/ASC-US guidelines.

Post-treatment followup. A third and less publicized potential use is in the followup of patients with high-grade squamous intraepithelial lesions after treatment with cone orLEEP. In recent years, many publications, especially in the European literature, have addressed this topic. No large U.S. study is available. Table 1 is a compilation of the data from pertinent studies. Although the sensitivity of high-risk HPV typing in the followup of HSIL is high, it is the negative predictive value of a negative HPV test in conjunction with a negative Pap test, that could be used to triage these patients to routine screening quickly. The patients with positive post-treatment HPV and/or cytology could be followed more closely or colposcopied if they continue to be positive.

Table 1

| Sensitivity and negative predictive value of HR-HPV typing status post-treatment of HSIL for recurrence/residual disease |
|---|---|---|---|---|---|---|---|---|
| Author | Country | Size | Sensitivity (%) | Negative predictive value (%) | Year published | Method of HPV typing |
| Chu | Taiwan | 46 | 96 | 99 | 1997 | PCR |
| Bolt | Netherlands | 43 | 100 | 99 | 2000 | PCR |
| Debarge | France | 205 | 100 | 100 | 2003 | HCII |
| Jan | Taiwan | 79 | 78.7 | 100 | 2001 | HCII |
| Zelikson* | Netherlands | 108 | 83 | 99 | 2003 | PCR |
| Nebelmann* | Netherlands | 184 | 90 | 99 | 2001 | PCR |


Table 2

| HR-HPV positivity (%) in endocervical glandular lesions |
|---|---|---|---|---|
| Author | Year published | AIS | Endocervical adenocarcinoma | HSIL |
| Nonnet | 1999 | 100 | N/A | 92 | PCR |
| Kneze | 2004 | 82 | 100 | 80 | PCR |
| Blankert | 2003 | N/A | 78 | 100 | PCR** |
| Pind | 2004 | 100 | 91* | N/A | PCR |

¢ Testing performed on paraffin-embedded tissue.

Conclusions

There is ample evidence in the literature to support the use of ASC-US triage as both a screening and diagnostic tool among patients who are at risk for developing HPV-related lesions of the anal canal. The approach to caring for these patients is multidisciplinary and involves clinicians from many different disciplines of medicine, including family medicine, internal medicine, infectious disease, dermatology, gynecology, surgery, and pathology. As our colposcopes and analytical techniques for the diagnosis of squamous intraepithelial lesions and squamous cell carcinoma in men have made great advances, colposcopy in the followup of squamous intraepithelial lesions in men is possible.

- A combination of negative high-risk HPV testing and a negative cytology should result in longer screening intervals, that is, three years.
- For cytology-negative, HPV-positive patients, repeat both in six to 12 months.
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Atypical endocervical lesions. The guidelines of the ASCCP do not recommend high-risk HPV typing for atypical endocervical cells, citing limited data. As per the current ASCCP guidelines, cases with a diagnosis of atypical adenocarcinoma undergo colposcopy and biopsy. However, as much data emerge, it appears that a compelling case could be made for testing in cases of atypical endocervical cells. Based on limited studies, 11-14 most if not all adenocarcinoma endocervical in situ are high-risk HPV-positive. The usual mucin-producing adenocarcinomas have a high rate of positivity in the 90+ percent range. Followup studies on atypical endocervical cells show squamous dysplastic lesions to be the most common histologic diagnosis. Table 2 is a compilation of the data from recent studies on high-risk HPV typing in glandular lesions with continued on page 52

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may have a warty or exophytic appearance. High-grade SIL may also be identified in the deeper portions of more typical condyloma and LSIL. 14 Anoscopic evaluation of the keratinized portion of the anal canal and the surrounding perianal skin should also be included. On keratinized epithelium, the anoscopic changes associated with SIL are similar to those seen on vulvar colposcopy. A digital examination of the anal canal should be included as an essential part of the complete evaluation.

Just as with high-grade cervical lesions, high-grade ASIL is utilized to prevent the development of invasive carcinoma. Ablative and excisional techniques, similar to those used for the cervix, are used. 2 For invasive cancers, early detection of anal carcinoma is essential because tumor size is such an important prognostic factor. 3 Tumors less than 2 cm are curable with local therapy in 70 to 90 percent of cases. The cure rate drops to 50 percent for tumors with nodal involvement or tumors greater than 5 cm.

- Goldie SJ, Knut KM, Weinstein MC, Freedberg KA, Palefsky JM. High-risk HPV testing in glandular lesions with continued on page 52

C. Mody, MD

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