The Management of ASCUS Cervical Cytologic Abnormalities and HPV Testing: A Cautionary Note

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A recently published study of the management of low-grade cytologic smears compared immediate colposcopy to human papillomavirus (HPV) triage and entry cytology smears (conservative management) as three triage techniques for managing atypical squamous cells of undetermined significance (ASCUS) smears (Atypical Squamous Cells of Undetermined Significance/Low-grade Squamous Intraepithelial Lesion Triage Study [ALTS]). The study reported a high sensitivity (96.3%) for HPV testing using hybrid capture 2 to detect cervical intraepithelial neoplasia (CIN) III. The authors concluded that HPV testing is a viable option for managing ASCUS smears. We have reviewed the published data from the ALTS trial and have found a large excess of colposcopies and biopsies in the HPV arm in comparison with the conservative management (cytology) arm. In addition, the ALTS trial quality control and pathology review results raise doubts about the diagnostic validity of the study to establish standards of clinical practice. Furthermore, until the 2-year follow-up analysis of the conservative management arm is completed to detect CIN III, a valid comparison between HPV triage and conservative management is not possible. We conclude that, based on published data, HPV testing for routine clinical management of low-grade cytologic abnormalities (ASCUS smears) is not warranted, and that HPV testing is currently an investigational tool. (Obstet Gynecol 2001;98:849–51. © 2001 by the American College of Obstetricians and Gynecologists.)

A number of years ago, the National Cancer Institute sponsored a multicenter trial to study the sensitivity and specificity of three different triage techniques in the management of low-grade squamous intraepithelial lesions (LGSIL) and atypical squamous cells of undetermined significance (ASCUS smears)—the so-called ALTS trial.[1] Approximately 7200 women with a cytologic diagnosis of LGSIL or ASCUS were to have been randomly assigned to: 1) immediate colposcopy; or 2) human papillomavirus (HPV) triage with repeat smear; or 3) conservative management with repeat cytologic smears only. Patients in arms 2 and 3 also underwent cervicography to decrease the chance that an invasive carcinoma was not missed. Smears were performed with a monolayer preparation (ThinPrep, Cytyc Corp., Boxboro, MA), and HPV testing was performed using the hybrid capture 2 (HC2, Digene Corp., Gaithersburg, MD) assay for oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) at the Food and Drug Administration's approved threshold of 1 pg HPV DNA/mL. The purpose of the trial was to evaluate the advantages and disadvantages of each technique as well as the effectiveness of HPV testing to identify women at increased risk for a serious lesion.

A preliminary analysis of the LGSIL portion of the study was previously reported[2] on 642 women and showed the prevalence of a positive HPV test was so great that the use of HPV testing as a discriminator for LGSIL was ineffective, and this portion of the trial was discontinued. The most recent report[3] was made after the results of the colposcopic and HPV arms were available for 3488 women with an initial diagnosis of ASCUS who were randomized to one of the three arms of the trial. Two-year follow-up on all subjects is to be done, but the results of this follow-up, including the ultimate effectiveness of the conservative management arm (repeat smear), were not available at the time of this initial analysis.

The results from each arm are shown in Table 1, which is adapted from the original article. As can be seen in the immediate colposcopy arm, 114 (10%) patients underwent loop electrosurgical excision procedure (LEEP). In the HPV arm, 611 (53%) patients underwent colposcopy, which led to 130 LEEP procedures. In the conservative management arm, colposcopy was done if the entry smear showed an LGSIL reading or worse. In this group, 94 (8%) patients were colposcoped, which resulted in 65 LEEP procedures. The full analysis of the conservative management arm will require the previously mentioned 2-year follow-up data. The authors of the ALTS report indicated that the HPV HC-2 test had an overall sensitivity of 96.3% to detect CIN III+, which led to the authors to conclude that HPV testing using

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Table 1. Yield of LEEP and CIN III for Patients Who Underwent Colposcopy in the ALTS Trial

Trial arm	Patients in study arm	Patients colposcoped/ patients in arm	LEEP performed/ patients colposcoped	LEEP not performed/patients colposcoped	CIN III+ diagnosed/patients colposcoped
Immediate colposcopy	1163	1149/1163 (99%)	114/1149 (10%)	1035/1149 (90%)	59/1149 (5%)
HPV triage	1161	611/1161 (53%)	130/611 (21%)	481/611 (79%)	77/611 (13%)
Conservative management	1164	94/1164 (8%)	65/94 (69%)	29/94 (31%)	44/94 (47%)

LEEP = loop electrosurgical excision procedure; CIN III = cervical intraepithelial neoplasia; ALTS = Atypical Squamous Cells of Undetermined Significance/Low-grade Squamous Intraepithelial Lesion Triage Study; HPV = human papillomavirus.

hybrid capture 2 is a viable (and presumably desirable) option to manage patients with an ASCUS smear. We believe a closer evaluation of their published data indicates that such a conclusion is not valid, and based on evidence currently available, the utility of HPV testing as an effective tool for clinical decision making regarding ASCUS smears has yet to be demonstrated.

There are numerous reasons for our concern about their conclusions. First, the study was designed as a follow-up study to compare the results of HPV testing with cytology follow-up. To report the results of the entry data as the authors have done may be very misleading and is potentially biased against cytology follow-up. It is certainly possible that when the trial is completely analyzed, the conservative management arm will identify a comparable number of CIN III as the other arms. Because the results the authors have published are not able to determine whether cytology follow-up is better or worse than immediate colposcopy or HPV triage (the stated purpose of the trial), the paper is of questionable validity.

Another measure of the effectiveness of HPV testing in arm 2 compared with conservative management in arm 3 is the evaluation of the specificity of HPV triage. Unfortunately, the authors of the ALTS report did not publish any estimates of specificity for either the HPV arm or the repeat conservative management arm.

We calculated the yield of LEEP and CIN III+ per colposcopy performed as an alternative outcome measure to compare the performance of arms 2 and 3, using data from the ALTS report (Table 1). The yield of LEEP after colposcopy in the HPV arm is 21% (130 of 611), whereas in the conservative management arm, it is 69% (65 of 94). The yield of CIN III+ after colposcopy in the HPV arm is 13% (77 of 611), whereas in the conservative management (cytology) arm, it is 47% (44 of 94). Thus, the highest proportion of high-grade lesions was diagnosed using colposcopy in the conservative management arm. The gain might be best understood conceptually by comparing the proportion of colposcopies that did not result in LEEP as a surrogate measure of specificity. Because colposcopy is an expensive test, the most desirable proportion is the lowest proportion of colposcopies. The value for LEEP in the HPV arm is 79% (481 of 611), whereas in the repeat cytology arm, it is 31% (29 of 94), a much more desirable result. Clearly, the conservative management arm provides the most efficient yield of CIN III+ for the number of procedures performed, reflecting the large number of patients who underwent colposcopy in the HPV arm who likely did not have any disease. The ultimate interpretation of these numbers depends upon weighing the questionable potential benefits of uncovering sooner more cases of a preinvasive disease against the burden of increased emotional and financial costs to the patient.

The fact that the conservative management arm identified fewer cases of CIN III+ at entry than the HPV arm is not a serious concern. As noted previously, 2-year follow-up data have yet to be analyzed. Presumably, additional CIN III+ cases will be found, particularly in the conservative management arm among the 999 remaining patients.

Harris also noted weaknesses in the published results of the ALTS trial and the fact of excess colposcopies in the HPV arm (Harris JE. Comparison of three management strategies for patients with atypical cells of undetermined significance: Baseline results from a randomized trial. JNCI 2001;93:950 [letter]). He estimated a specificity for the HPV arm of 53.4% and a specificity of 79.4% for the entry data of the conservative management arm. It should be noted that for a single screening test, greater sensitivity can only be achieved by sacrificing specificity. However, when comparing two different screening tests, one test may have advantages in both sensitivity and specificity over the other. In the ALTS trial, the HPV triage protocol has very high sensitivity but poor specificity, whereas the conservative management arm has much better specificity and may achieve a better balance of sensitivity and specificity, particularly when the 2-year follow-up data are analyzed. Strickler and Shah also noted concerns about the results of the ALTS trial and the excessively positive interpretation that appeared in the lay press (Strickler H, Shah K. Comparison of three management strategies for patients with atypical cells of undetermined significance: Baseline results from a randomized trial. JNCI 2001;93:951 [Letter]). They noted

that better results might have been seen if older patients were evaluated (over age 30) because younger patients are so frequently positive for HPV. A similar concept was advanced by Rebello et al[4] who suggested that a positive HPV test in those over age 30 would likely be more useful than a positive test in younger individuals, whereas a negative test in individuals under age 30 could indicate the need for less frequent cytologic screening. All of these considerations confirm that HPV testing is currently an investigational tool.

An additional substantial concern is that the quality control committee of the ALTS trial confirmed an ASCUS diagnosis in only 55% of the cases, downgraded 31% and upgraded 14%. The latter indicates that some patients who were in the trial had a more severe diagnosis than ASCUS.[3] This was further substantiated in the pathology study of Stoler and Schiffman.[5] These authors reevaluated the cytologic and histologic diagnosis of 4948 monolayer cytologies, 2237 colposcopic biopsies, and 535 LEEP procedures for the entire ALTS trial. They calculated a κ statistic to compare the diagnosis from each center with the final diagnosis of the panel of reviewers. In general, they noted a κ statistic of 0.8 or higher shows substantial agreement. The cytologic and pathologic reading at each center showed, in general, more serious disease than the diagnosis of the reviewers. Furthermore, the κ statistic calculated to 0.46 for cytology and biopsy, and 0.49 for LEEP, which indicates only moderate agreement. Thus, for these analyses of low-grade lesions, as was done in the ALTS trial, the validity of the various diagnoses on which the entire trial was based is open to question, particularly regarding the overall applicability of the results to clinical practice. What would be of greater value would be more stringent criteria and less frequent diagnosis of the ASCUS category. This seems particularly relevant because it is a cytologic term and not as widely used outside the United States.

As previously noted, a complete analysis of the trial will not be possible until the 2-year follow-up data are analyzed. However, based on the currently published data, it is clear an excess and probably unnecessarily high number of procedures occur in the HPV arm. Because the ultimate goal of any intervention program is the prevention of invasive cancer, it would have to be shown that this aggressive effort to uncover and treat CIN III+ with HPV testing is effective in preventing invasive cancer among screened populations in comparison with the conservative management group. We are not aware of any data to support such an aggressive approach. There is reasonable doubt that such a demonstration will be accomplished, particularly because it is known that many low-grade lesions spontaneously regress, and even among high-grade squamous intraepithelial lesions, some will spontaneously regress.[6–8]

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