

Management of ASCUS/ LSIL Pap Smears
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Epidemiology

- * Approximately 55 million Pap smears are performed in the United States each year
- * About 5% are interpreted as atypical squamous cells of undetermined significance (ASCUS) and 2% are interpreted as low-grade squamous intraepithelial lesion (LSIL).
- * Accounts for over 2 million ASCUS pap smears and over 1 million LSIL pap smears each year

Significance of ASCUS/LSIL

- * Risk of having high-grade disease or cancer:
- * ASCUS- 8-20%
- * LSIL- 10-30%
- * Even though each of these categories has a relatively low to moderate risk of having high-grade disease or cervical cancer, because of the commonness of these Pap smear readings they result in 70% of all high-grade lesions being detected.

What to do about it?

- * Clinical Dilemma
- * No universal agreement exists for the management of LSIL or ASCUS.
- * Most low-grade lesions will regress spontaneously and many equivocal lesions will be shown to be benign.
- * Management is difficult because of the concern of missing the small but important subset of women that have a high-grade disease or cancer while not doing unwarranted testing on everyone.

Importance of HPV

- * The discovery of the role of HPV in cervical cancer can help aid in the management of ASCUS/LSIL pap tests.
- * HPV causes virtually all cases of preinvasive and invasive cervical cancer.
- * Also the type of HPV (low risk or intermediate/high risk) is associated with the severity of squamous intraepithelial lesions and their natural history.
- * Low Risk HPV Types: 6,11,42,43,44
- * High Risk HPV Types: 16,18,31,33,35,39, 45,51,52,56,58,59, and 68.

Management of ASCUS/LSIL

- * The need for clear management guidelines with ASCUS and LSIL was discussed at the 1991 Bethesda Workshop.
- * This led to a National Cancer Institute-sponsored workshop to discuss the ability to conduct a RCT to outline the viable management strategies.

The Start of the ALTS Trial

- * Although they disagreed as to the proper management approach, they did agree as to the main possible choices that merited consideration:
immediate colposcopy, cytologic follow-up, and triage using HPV DNA testing.
- * Hence the National Cancer Institute initiated the ASCUS-LSIL Triage Study (ALTS).
- * The largest and most costly single clinical trial in the prevention or treatment of cervical carcinoma.

ALTS Study

- * It involved 4 clinical center and all women had a community-read cytology result of ASCUS or LSIL.
- * 5060 women were enrolled: 3488 with ASCUS and 1572 with LSIL
- * They were then randomly assigned to one of the three management arms:
immediate colposcopy, HPV triage with colposcopy with positive HPV testing, and
conservative management with colposcopy if cytology was HSIL.
- * All women had follow-up cytology at 6 month intervals for 2 years.
- * HPV testing was performed using ThinPrep vials.
- * At the end of the 2 year study period, all women underwent colposcopy.
- * One to ensure patient safety
- * Two to provide complete certainty of disease end points (CIN 2 or 3) prior to exiting the study.
- * The clinical endpoint chosen to be studied was the identification of CIN3 or greater.
- * The main study endpoint of histologically confirmed CIN3 was chosen because there is a general consensus that this lesion is at high risk of progressing to invasive cancer and requires definitive treatment.
- * LEEP procedure was performed on women with CIN 2 or 3 grade lesions on colposcopically directed biopsy.
- * LEEP was also offered to women with a persistent low-grade lesion if the colposcopically directed biopsy at exit showed CIN 1 and cytology results from at least one of the previous two visits showed LSIL or HPV + ASCUS.

ALTS Study-ASCUS Study Arm

- Comparison of diagnosis of CIN 2 or 3 by study arm

	IC	HPV triage	CM	P value
CIN 2	92 (7.9%)	85 (7.3%)	55 (4.7%)	.005
CIN 3	97 (8.3%)	101 (8.7%)	108 (9.3%)	.72
CIN 2 & 3	189 (16.2%)	186 (16.0%)	163 (14%)	.26

ALTS Study-ASCUS Study Arm

- Cumulative diagnosis of CIN 3 by study arm

	IC	HPV triage	CM
Enrollment	58 (59.8%)	76 (75.2%)	44 (40.7%)
Follow-up	14 (14.4%)	6 (5.9%)	22 (20.4%)
Exit	25 (25.8%)	19 (18.8%)	42 (38.9%)

ALTS Study-ASCUS Study Arm

- Identification on CIN 3 by initial test

	IC	HPV triage	CM
Sensitivity for CIN 3	53.6%	72.3%	54.6%
Referral to colposcopy	100%	55.6%	12.3%

ALTS Study-ASCUS Study Arm

- Estimated triage test performance on dx of CIN 3
 - For these estimates, missing test results, missed visits, and the timing of visits were ignored to focus on the performance of the tests based on how many were completed.

	Sens. CIN 3	Referral
Enrollment HPV	92.4%	53.1%
ASCUS x 1	83.4%	58.1%
ASCUS x 2	95.4%	67.1%
ASCUS x 3	97.2%	72.7%

ALTS Study-ASCUS Study Arm

- * Need to repeat cytology twice at 6 month intervals at ASCUS threshold to provide a comparable sensitivity for detection of CIN 3 with an increase in referrals to colposcopy.
- * Clinical Endpoint was identification of CIN 3+
 - testing for HPV with referral to colposcopy if positive for high risk HPV identified 92.4% of women with CIN 3+ and referred 53.1% of the population to colposcopy.
 - a repeat cytology using a threshold of HSIL identified 44% of women with CIN 3+ and referred 8%. A lower cytology triage threshold of ASCUS identified 83.4% while referring 58.1%.
- * Serial cytology with an ASCUS threshold required two visits to achieve similar sensitivity of 95% to the HPV triage strategy while then referring 67% of women to colposcopy.
- * The immediate colposcopy group was only 54% sensitive and referred 100% of women to colposcopy.
- * Of the total CIN 3 lesions, those in the HPV triage were diagnosed the earliest followed by the immediate colposcopy arm.
- * 11 cases on CIN 3 were found only by offering LEEP to women with persistent low-grade lesions.
- * One-half of the LEEPs performed in the IC and HPV triage were performed at the time of enrollment compared to one-quarter of the LEEPs performed in the CM arm.
 - * ALTS data demonstrates that HPV triage is at least as sensitive as immediate colposcopy in the detection of CIN 3 while nearly halving the number of women referred for colposcopy
- * Repeat cytology with referral at an ASCUS threshold is also as sensitive but requires more office visits and leads to more colposcopic examinations.
- * HPV triage particularly when liquid-based cytology permits reflex HPV testing of a single cytology specimen.

- * All three approaches are equally effective in detecting CIN 2 and CIN 3 after 2 years.
 - disadvantages to repeat Pap testing include a significantly higher referral to colposcopy, more office visits, more expensive, and delayed detection of CIN 3.

American Society of Colposcopy and Cervical Cytology Guideline

* Guideline was released in April 2002.

* A program of repeat cervical cytological testing, colposcopy, or HPV triage are all acceptable methods of managing women with ASCUS.

- when liquid-based cytology is used or co-collection for HPV DNA testing is done, reflex HPV testing is the preferred approach.

- all women who test positive for high risk HPV should undergo colposcopy.

- test positive but do not have biopsy confirmed CIN can include repeat cytological testing at 6 and 12 months with referral back to colposcopy if a result of ASCUS is obtained.

- women who test negative for high risk HPV can be followed up with repeat cytological testing at 12 months.

ALTS Study-LSIL Study Arm

* The HPV triage arm for the subset of women with LSIL was closed early because an interim analysis showed that 83% of these women would be triaged to colposcopy. The results demonstrated limited utility of the HPV assay to direct management decision for LSIL because of the substantial majority that are referred to colposcopy.

Review of Abnormal Pap Smears at UNDFPC

* 47 charts with a diagnosis of abnormal pap smear were reviewed

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	Number	(%)
ASCUS	32	70.2
LSIL	11	21.3
HSIL	3	6.4
Benign cellularity	1	2.1

Management Of ASCUS

Repeat Pap with no HPV testing	17/32	53.1%
Repeat pap with HPV testing	4/32	12.5%
Reflex HPV	11/32	34.4%

Management of ASCUS with Reflex HPV testing

- * 11 of 32 cases of ASCUS underwent reflex HPV testing.
- * 7/11 cases were positive for high/intermediate risk of HPV. 100% underwent colposcopy.
- * 4/11 cases were negative for HPV. 75% (3/4) underwent repeat pap smears at varying schedules ranging from 3-4 months. 25% (1/4) underwent colposcopy for recurrent ASCUS pap smears.

Management of Repeat Pap with HPV testing on Repeat Pap Smear

- * 4 out of 32 underwent repeat pap smears with subsequent HPV testing
- * 1/4 was negative for HPV and underwent repeat pap smears
- * 3/4 were positive for high/intermediate risk HPV and all 3 underwent colposcopy

Faculty vs. Residents

- * Of the 32 ASCUS pap smears reviewed, 14/32 (43.8%) were resident patients. 18/32 (56.2%) were faculty patients.

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	Residents	Faculty
Repeat Pap with No HPV testing	42.9 % (6/14)	61.1% (11/18)
Repeat Pap with HPV testing	14.3% (2/14)	11.1% (2/11)
Reflex HPV	42.9% (6/14)	27.8% (5/18)

Management of LSIL

- * 11/47 patients had a diagnosis of LSIL on pap smear
- * 100% of these patients underwent colposcopy.
- * 4/11 had reflex HPV testing
- * According to the ALTS study, reflex HPV testing is unwarranted in this subset of patients as it would not impact the approach to treatment.

Management of HSIL

- * 3/47 patients had a diagnosis of HSIL on initial pap smear
- * 100% underwent colposcopy
- * 0/3 had HPV testing.

Highlights

- * The most effective and least costly approach to ASCUS result is to perform reflex HPV testing.
- * Patients with a positive result should undergo colposcopy.
- * Patients with a negative result may wait a year to undergo a repeat pap smear.
- * Patients with a diagnosis of LSIL on a pap smear should undergo colposcopy without the need to perform HPV testing prior.

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