

CAP-ASCCP LAST Work Group 2: Terminology for Intraepithelial Lesions, Integrating Morphology, Biology, and Clinical Management

Background

Working Group 2 (WG2) was tasked with evaluating the current diagnostic terminology utilized for non-invasive HPV-related squamous lesions of the lower anogenital track and determining if terminology could be clarified and unified. A second task was to assess the use of molecular markers in conjunction with histomorphologic assessment. For the purpose of literature review, WG2 was split into 3 subgroups: cervix/vagina, vulva/penis and perianus/anus. **In doing so, over 1700 articles were identified from a comprehensive literature search. Via inclusion and exclusion criteria for the title/abstract and full text reviews, this number was culled to 182, from which final data extraction was performed. (Note: Formal grading of the evidence was not performed for WG2 but is planned for WG4. Expert consensus is provided)** The vast majority of the articles dealt with cervix/vagina; however there were some articles that did address vulva/penis and anus/perianus.

1. What is the current state of clinical management based upon histomorphologic diagnosis?
 - a. The articles identified in a comprehensive literature review did not directly address this question.
 - b. The current state of clinical management for cervical/vaginal disease is based on guidelines from the ASCCP and ACOG and on the existing 3-tier CIN/VAIN terminology. The current ASCCP / ACOG guidelines for treating vulvar disease are based on ISSVD nomenclature with essentially 2 tiers, namely condyloma and VIN.
2. What are the areas of potential overlap in histopathologic terminology (cytology, dermatopathology, GYN pathology)?
 - a. Based on our literature search there is overlap between Bethesda cytology nomenclature ("Bethesda"), dermatopathology terminology, and the most common terminology used in surgical pathology practice for all areas of the lower anogenital track.
 - b. There are institutions that use cytology terminology i.e. Bethesda or a modified Bethesda nomenclature during histomorphologic diagnosis.

3. What are the possibilities of integrating cytology, histopathology, molecular findings, and clinical terminology? (molecular issues in conjunction with WG4)

Summary from WG-4:

A. Is any marker ready for primetime use, meaning it should be used commonly and reliably to refine diagnostic issues?

- p16 is the only marker with sufficient data available to allow an analysis for use in lower anogenital tract specimens. ProExC and Ki67 have similar trending data, but their accumulated data are insufficient to make an independent recommendation for use, alone or in combination (see below).

- Although only a few studies are available that focus on body sites other than cervix all of these studies show results similar to cervix, and hence, given the underlying similarities in HPV-associated biology in all lower anogenital tract sites, WG4 concludes that their recommendations are applicable across all lower anogenital tract sites.

Note: These data and recommendations do not apply to non HPV-related precancerous lesions (e.g. simplex VIN)

B. What are the recommendations to clarify the histologic terminology, based on molecular marker input?

- Based on the evidence reviewed, WG4 cannot make a recommendation for or against a 2-tier or 3-tier nomenclature system based on histologic evaluation alone. The work group does note that while all the marker studies examined were neutral or supportive of a two tier system/biology, they could find no positive marker based studies to support a distinct 3 tier biology. WG4 also notes in their recommendation #2 that p16 is recommended to clarify intermediate category biopsies (i.e. CIN 2) into either a low grade or precancerous lesion. Thus, use of p16 effectively leads to a 2-tier classification system in this particular circumstance.

C. For low grade and high grade disease (CIN1 vs CIN 2/3), will any molecular marker be definitional for high grade?

- Based on the available data, WG4 concludes that there is insufficient evidence to prospectively make a determination of high vs. low grade disease based solely on a p16 result. In

particular, the natural history of CIN1 adjudicated by p16 is uncertain and critically needs further study. Hence, at present, no recommendation can be made for or against the use of p16 for this purpose. As noted above (WG4 recommendation #2), p16 has utility in making the distinction between a low grade lesion and high grade lesion only in the circumstance in which an equivocal lesion, i.e. CIN2 is under consideration based on the H&E morphology.

- WG4 also notes that if the pathologist's histologic diagnosis is "obvious" CIN1 they do not recommend further immunohistochemical studies.

D. For those studies involving multiple markers, is a combination of markers equivalent or better than a single marker?

- Based on the available data, WG4 concludes that the evidence does not support any combination of markers to substantially improve performance when compared to the use of p16 alone.

4. Based on the possibilities, what is the recommendation to clarify the histopathologic terminology?

From review of the articles by WG2 and WG4, data on the natural history of anogenital HPV-associated lesions at sites other than the cervix are limited, but the biology of HPV-related noninvasive squamous lesions appears to have a similar natural history. The HPV virotypes associated with high-grade intraepithelial disease are also similar across all sites. (REFIDS to be added)

Recommendation #1:

Expert consensus: Due to the similarity of HPV-related squamous proliferations across the lower anogenital tract, a unified nomenclature is recommended for all HPV-related preinvasive squamous lesions in these areas.

Note: Non-HPV-related squamous lesions should have a separate distinctive nomenclature. i.e. differentiated VIN in the vulva.

Recommendation #2:

Expert consensus: A single set of diagnostic terms (nomenclature) should be used for preinvasive HPV-related squamous lesions of the

lower anogenital tract. From the literature review of both WG1 and WG2, it is clear that there are multiple terminologies currently being used in the histopathologic diagnosis of HPV-related squamous lesions of the cervix, vagina, anus and vulva. This leads to confusion about what the terms mean and how to develop appropriate treatment guidelines.

Recommendation #3:

Expert consensus: A 2-tiered nomenclature is recommended for preinvasive HPV-related squamous proliferations of the lower anogenital tract.

Rationale/Evidence:

A. While WG4 could not make a recommendation for or against a 2-tiered or 3-tiered nomenclature system based on microscopic evaluation alone, they could find no positive molecular marker-based studies to support the conclusion that 3-tiered biology exists. They also found that the use of p16 to potentially upgrade or downgrade equivocal (CIN2) lesions (refer to WG4 recommendation #2) effectively leads to a 2-tiered classification system.

B. From the literature search, there is weak evidence that a 2-tiered system for cervical disease is more reproducible (with higher kappa statistics). There are few data regarding anal or vulvar/penile disease. It is most likely that the higher kappa statistics are due to the decreased number of categories rather than distinctive histopathologic features in studies assessing 2-tiered systems.

- i. For 2 tiers (Bethesda): Kappa statistics from .30 to .71 (RFID 1204, 1210, 2252, 3105, 3174) Studies are cases series or cross sectional with low numbers other than 3174 from the ALTS studies which has high numbers and is a blinded study comparing 2 expert panel groups.
- ii. For 3 tiers (CIN): Kappa statistics from .12 to .58 (RFID 2350, 2369, 2354, 3044, 3090, 3105) All studies are case series or cross sectional and low numbers

C. Expert opinion suggests that CIN2 actually represents a mixture of low-grade (risk) and high-grade (risk) lesions with borderline histopathologic features between classic CIN1 or condyloma and CIN3. This is one of the least reproducible categories and the intermediate risk of progression is seen because it actually represents this mixture of low and higher risk patients rather than a biologically distinct category.

D. Recent textbooks (Blaustein's Pathology of the Female Genital Tract [Kurman, Ellenson, Ronnett], Crum and Lee and the AFIP fascicle) have recommended a 2-tier system for cervix/vagina lesions.

E. The ISSVD recommended terminology for vulvar HPV-related squamous lesions is essentially a 2-tiered system with the older term VIN1 relegated to condyloma.

- A potential negative aspect to this recommendation is that the clinical guidelines for treating cervical lesions are based on a 3-tier (i.e. CIN) system.

Recommendation #4:

No consensus opinion was generated regarding new terminology. It is important as noted by WG1 and stated many years ago by Dr. Drake as the Chair of the IAC terminology committee, that any new nomenclature should "improve understanding between pathologists as well as between pathologists and clinicians. It should embrace the known biology of the morphology and should try to incorporate all the known morphologies. The construction of an ideal classification system should not be seen as a challenge to tradition, or to science, but as an exercise in logic and semantics".

Given those ideals, WG2 requests feedback on the following potential terms:

Within the Survey, you will be asked as to your preference on the following recommended terminologies (please select only one preferred terminology or free-text other suggestion):

1. Low Grade HPV-Associated Squamous Intraepithelial Lesion (LHIL)
High Grade HPV-Associated Squamous Intraepithelial Lesion (HHIL)
2. Low Grade Squamous Intraepithelial Lesion (LSIL)
High Grade Squamous Intraepithelial Lesion (HSIL)
3. Squamous HPV Viral Cytopathic Lesion
Squamous HPV Associated Dysplasia (SHAD)
4. Condyloma

Cervical/Vaginal/Vulvar/Anal/Penile Intraepithelial Lesion

5. Low-grade Intraepithelial Abnormality (LGIA)
High-Grade Intraepithelial Abnormality (HGIA)

6. Other (free text):

Note: If a 2-tiered system is not decided upon at the voting session at the LAST Consensus Conference, two alternatives would be:

1. Use a 2-tier system with an intermediate (uncertain) category similar to ASC-H for those lesions in the gray zone between low grade and high grade. P16 or equivalent markers would be used as recommended by WG4 to try to limit the use of this category.

2. Maintain a 3-tier system and use current IN terminology. It would be recommended to attempt to limit the number of IN2 diagnoses through the use of p16 or equivalent marker studies.

5. Based on the recommendations, what are the criteria that define the histopathologic criteria?

These criteria are still to be determined based on the final recommendation for nomenclature

6. Based on the criteria, what are the differences that effect clinical management that the clinicians need to know?

If a 2 tier system is suggested new clinical guidelines would be needed to determine what to do with patients from the old CIN 2 category.

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