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The LAST Project and its Implications for Clinical Care

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Abstract

Despite the histologically identical nature of lesions, multiple complex terminologies and historically meaningful eponyms have been developed to describe this pathologic and clinical spectrum of disease for the purpose of patient management. Based on a growing recognition of a need for unified terminology the American Society for Colposcopy and Cervical Pathology and the College of American Pathologists Pathology and Laboratory Quality Center jointly convened a process to tackle this challenge. The Lower Anogenital Squamous Terminology (LAST) Project was designed to reassess and harmonize the terminology used to describe human papillomavirus-associated squamous lesions of the lower anogenital tract as manifested in a variety of end organs including the cervix, the vagina, the vulva, the perianus, the anus, the penis, and the scrotum. The clear unambiguous distinction between cancer precursors and those without malignant potential inevitably leads to greater consistency in the interpretation of management guidelines, and the therapeutic options offered to patients.

Keywords

Squamous intraepithelial lesion; human papillomavirus; lower anogenital tract; terminology

Introduction

Terminology for lower anogenital tract (LAT)-associated pre-malignant disease historically developed along two separate paths depending on whether the epithelial lesion was mucosal or cutaneous.[1] The terminology of mucosal cervical, vaginal, and anal lesions was developed by general pathologists, gynecologic pathologists, and gynecologists. By contrast terminology for cutaneous vulvar, penile, and perianal lesions was mostly developed by dermatologists and dermatopathologists. These conventions evolved over more than a century and certainly antedate our improved understanding of the etiologic role of human papillomavirus (HPV), related disease processes and a broader range of treatment options. These differing terminologies, for lesions now recognized to be biologically similar create the potential for miscommunication between and among pathologists seeking to reconcile

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the various terminologies with clinically identified lesions while clinicians must make patient management decisions based on pathologic assessments.

Since Zur Hausen first proposed the etiologic link between human papillomavirus and cervical cancer, there has been a growing recognition of the role of this viral infection in other epithelial neoplasias including those of the vagina, vulva perineum, anus as well as the penis and scrotum. It is now generally accepted that HPV infection in most end organ may follow two possible pathways. One supports virion production but may or may not necessarily lead to the development transient lesions not destined for invasion. These processes may be known by a variety of terms including cervical intraepithelial neoplasia (CIN) 1, mild dysplasia, low grade squamous lesions, or in specific cases condyloma. In the alternate pre-neoplastic pathway there is a loss of control between viral oncogene expression and epithelial differentiation. The products of this viral oncogene over expression leads to cell proliferation and clonal expansion of relatively undifferentiated cells by viral replication and the development of the truly pre-malignant lesion. These processes are similar across tissue types and regardless of sex of the individual and support for a unified etiology for HPV related squamous neoplasia.

Despite the histologically identical nature of these lesions multiple complex terminologies and historically meaningful eponyms have been developed to describe this pathologic and clinical spectrum of disease for the purpose of patient management.

Historical Context

Intraepithelial precancer was first described in 1888 by Sir John Thomas.[2] With subsequent descriptions as surface carcinoma or intraepithelial carcinoma and later carcinoma in situ (CIS), treatment became increasingly dependent of histopathologic assessment.[3-5] The term carcinoma in situ led to a clinical management approach of hysterectomy for women with CIS, reserving more conservative approaches for those without CIS. By the 1950s other terms came into usage for surface lesions that had less risk of progressing to cancer than CIS. Initially termed “anaplasia” and “atypical hyperplasia” these terms were subsequently replaced by the more widely accepted “dysplasia”.

The largest change in cervical histologic terminology came in 1969 when cervical carcinogenesis was proposed as a continuum of disease ranging from mild dysplasia to invasive cervical cancer.[6] CIN was coined to emphasize its status as a precursor to invasive cervical cancer. Under this nomenclature dysplasias were termed: mild dysplasia – CIN I; moderate dysplasia – CIN II; and severe dysplasia – CIN III.

As the biology of HPV infection and its relationship to and cervical oncogenesis was increasingly understood by the 1980s, the subjectivity of the differentiation between CIN 2 and CIN 3 became more apparent. This led to numerous proposals to replace the 3-tiered CIN system with a 2-tiered system of low-grade and high-grade intraepithelial lesions (LSIL and HSIL) similar to cytology terminology of the 1988 Bethesda System.[7, 8] However, such a 2-tiered nomenclature for histopathology was not widely adopted in the 1990s and lacked the support of most professional organizations.[1]

The 2001 and 2006 ASCCP Consensus Guidelines for the clinical management of cervical histological abnormalities began to move toward a 2-tiered nomenclature for cervix using the terms CIN1 and CIN2,3. The exception was for disease in adolescent and young women where the differentiation between CIN 2 and CIN 3 was preserved.[9, 10]

In the 1990s two important changes occurred in the management of CIN. Expectant management became the primary follow up for CIN 1. This was based largely on increasing

appreciation for the transient nature of most of these lesions. By contrast in-office excision of the transformation zone using the loop electrosurgical excision procedure (LEEP) became the principal management for precancer lesions (CIN 2, 3) across the US and much of the developed world.[11] During the last decade there has again been a renewed interest in 2-tiered low-grade and high grade nomenclature that better reflects the natural history of lower anogenital tract HPV associated intraepithelial lesions. The LAST conference was an attempt to systematically reassess the latest data in an effort to develop to a broad consensus across specialty groups and stakeholders for this change in nomenclature.

The LAST Process

Based on a growing recognition of a need for unified terminology the American Society for Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP) Pathology and Laboratory Quality Center jointly convened a process to tackle this challenge (the details of which can be found at <http://links.lww.com>). This 14 month process brought together a broad array of 53 experts and opinion leaders from a variety of clinical and scientific disciplines. Five Work Groups (WGs) (TABLE 1) were assembled to conduct systematic reviews of the relevant literature and discussions of the relevant issues, and the process culminated in consensus conference in March of 2012.

The Lower Anogenital Squamous Terminology (LAST) Project, conceived and sponsored by the CAP and the ASCCP, was designed to reassess and harmonize the terminology used to describe HPV-associated squamous lesions of the LAT as manifested in a variety of end organs including the cervix, the vagina, the vulva, the perianus, the anus, the penis, and the scrotum.[1]

The primary goals of the last process were to accomplish the following: 1) Standardize the terminology used for reporting histopathology diagnoses of HPV-related muco-cutaneous squamous lesions of the lower genital tract, including intraepithelial lesions and minimally invasive cancers (but excluding non-HPV related dermatologic and vulvar lesions). 2) Harmonize terminology across the various lower anogenital tract sites using current evidence-based knowledge regarding the biology of HPV-related squamous lesions and their clinical management. 3) Harmonize the terminology for histopathology with the Bethesda System for reporting gynecologic and anal cytology (if applicable). 4) Assess the use of new technologies to validate proposed terminology standards, and provide guidelines for appropriate use. This work was conducted primarily by five working groups comprised of content experts and representatives from a range of professional societies and stakeholder groups (TABLE 1).

The recommendations of the LAST conference and the background documentation are detailed in a pair of simultaneously published papers in the October issues of Lower Genital Tract Disease[1] and the Archives of Pathology[12]. Supporting documentation and related material are included in electronic appendices that can be accessed from the journal websites.

Findings and Recommendations of the LAST Conference

The LAST Conference findings support a single unified histopathologic two-tiered nomenclature with a single set of diagnostic terms; specifically LSIL and HSIL. This can be further qualified using the –IN terminology to facilitate clinical management.

Immuno-histochemistry p16 testing is recommended when a diagnosis of –IN 2 under the old terminology or to help adjudicate cases of disagreement between pathologists. A strong diffuse positive staining pattern is consistent with the HSIL diagnosis, while a negative

staining supports the LSIL diagnosis or a non-HPV etiology. Another clinically important innovation is the development of the term superficially invasive squamous cell carcinoma (SISCA) for minimally invasive squamous cancers of the lower anogenital track that is completely excised and potentially amenable to conservative therapy. In the cervix this translates to a lesion that is not grossly visible, has invaded <3mm from the basement membrane, has a horizontal spread of <7mm, AND has been completely excised. Relevant variations of this terminology are described for the anal canal, vulva, and perianus.(TABLE 2)

TABLE 2 lists the recommendations of WGs 2, 3, and 4. WG2 put forth three recommendations. Their first recommendation supports a unified histopathologic nomenclature with a single set of diagnostic terms recommended for all HPV-associated preinvasive squamous lesions of the LAT. Their comprehensive literature review and expert opinion support the biologic and morphologic equivalence of HPV-associated squamous proliferations across the LAT. Given this equivalence, a unified histopathologic nomenclature is recommended for all HPV-associated preinvasive intraepithelial squamous lesions in the LAT. Biomarker characteristics, as noted by WG4, are also consistent across LAT sites, lending further support to this recommendation.

WG2's second recommendation was for a 2-tiered nomenclature for noninvasive HPV-associated squamous proliferations of the LAT, which may be further qualified with the appropriate –IN terminology. (–IN refers to the generic intraepithelial neoplasia terminology, without specifying the location. For a specific location, the appropriate complete term should be used. Thus, for an –IN 3 lesion: cervix = CIN 3, vagina = VaIN 3, vulva = VIN 3, anus = AIN 3, perianus = PAIN 3, and penis = PeIN 3). Rationale for this recommendation is that current understanding of HPV biology does not support a progressive 3-tiered system of mild, moderate, severe dysplasia/CIS or –IN 1, 2, 3. Rather, there is support for a dichotomous separation of morphologic designations that reflect transient active HPV replication and persistent HPV-associated precancer. On the basis of the comprehensive literature review by WG4, no biomarker data supported a 3- tiered system (see below). Instead, data are consistent with a 2-tiered system with low-grade lesions that are generally self-limited HPV infection and high-grade lesions that have the potential to progress to invasive carcinoma. The equivocal nature of the diagnosis of –IN 2, an intermediate category that has no biologic correlate, is thought to represent a mixture of low-grade and precancerous disease that cannot be reliably distinguished based on hematoxylin and eosin (H&E) morphology [13, 14]. The –IN 2 category is not a reproducible histologic category among pathologists. Studies of diagnostic concordance demonstrate considerable interobserver variability reflected in very low [kappa] statistics[13]. As might be expected from this mixture of high- and low-grade lesions, the risk of progression for lesions classified as –IN 2 is intermediate between –IN 1 and –IN 3. In addition, a substantial proportion of CIN 2 is found to represent CIN 3 on follow-up [15]. The recommendation for a 2-tiered system also harmonizes LAT terminology with other published systems, including those of recent textbooks and professional societies [16-20].

WG2's third recommendation was that the terminology for HPV-associated squamous lesions of the LAT as low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL), may be further classified by the applicable –IN sub-categorization. This recommendation harmonizes the descriptive terminology for cytology and histopathology for biologically similar HPV-associated squamous lesions of the LAT. This terminology is also the one used for 2-tiered histologic systems in recent textbooks published in the field [18-20]. In addition, this terminology was the most widely supported by responses during the open comment period and at least a 67% supermajority of the participants at the consensus conference.

WG3 reviewed data across LAT sites to recommend specific terminology for minimally invasive squamous cell carcinoma (SCC). They delineated 10 recommendations. As described earlier, a key recommendation was the term SISCCA for minimally invasive squamous cell carcinoma of the LAT that has been completely excised and is potentially amenable to conservative surgical therapy.

Recommendations 2 and 3 deal with specific parameters of defining a case of SISCCA. Recommendation 2 is for cases of invasive squamous carcinoma with positive biopsy/resection margins. It is recommended that the pathology report state whether the examined invasive tumor exceeds the dimensions for SISCCA or the tumor component is less than or equal to the dimensions of SISCCA and conclude that the tumor is at least a superficially invasive carcinoma. Recommendation 3 is for cases of SISCCA, parameters should be included in the pathology that report the presences or absence of lymph-vascular invasion (LVI) and the presence, number, and size of independent multifocal carcinoma.

Recommendations 4, 5, 6, 7, 8, 9 and 10 provide site specific recommendations. Specifically, SISCCA of the cervix, vagina, anal canal, vulva, penis, scrotum, and perianus. It is generally thought that all SCCs of the cervix are attributable to HPV [21]. SISCCA of the cervix is defined as an invasive squamous cell carcinoma that is no a grossly visible lesion and has an invasive depth of ≤ 3 mm from the basement membrane of the point of origin and has a horizontal spread of ≤ 7 mm in maximal extent and has been completely excised. Recommendations 5 and 9 are in actuality that there is no recommendation for early invasive squamous carcinoma of the vagina and scrotum, respectively. This owes to the rarity of primary SCC of the vagina and scrotum, and insufficient data to define early invasive squamous carcinoma in this site. Recommendation 6, 7, 8, and 10 provide parameters for site specific definitions of SISCCA for anal canal, vulva, penis, and perianus, respectively.

WG4 described four recommendations dealing with the use of molecular biomarkers in HPV-associated lower anogenital squamous lesions. Recommendation 1 stated that p16 IHC is recommended when the H&E morphologic differential diagnosis is between precancer and a mimic of precancer. Strong and diffuse block-positive p16 results provide support in a categorization of precancerous disease. Recommendation 2 was that if the pathologist is entertaining an H&E morphologic interpretation of -In 2 under the old terminology, p16 IHC is recommended to help clarify the diagnosis. Recommendation 3 states that p16 is recommended for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion. Recommendation 4 is a recommendation against the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with interpretations of negative, -IN 1, and -In 3.

WG5 was tasked with communication strategies to disseminate the work of the LAST Terminology and promote the uptake of its recommendations. Communities of interest were identified for the LAST Project. These included patients and patient advocacy groups, pathologists, gynecologists, primary care providers, dermatologists, infectious disease specialists, colorectal surgeons, urologists, nurse practitioners, and other allied health professionals and government, regulatory, and nomenclature agencies. Specific actions recommended by WG5 include support for guideline publications, promotion of editorial commentaries for journals in related fields, presentation of summary recommendations at scientific meetings, educational materials, and development of a web site that would include reference images, sample reports, and a self-test.

Conclusions

The clarification of this terminology is not simply an esoteric exercise but instead it is critical to clinicians and patients alike. The historic heterogeneity of clinical and histopathologic terminology has led to inevitable diagnostic variation and miscommunication between those taking the biopsies and those interpreting the findings; this in turn has important implications for the treatment, follow-up and prognosis of these lesions. The clear unambiguous distinction between cancer precursors and those without malignant potential inevitably leads to greater consistency in the interpretation of management guidelines, and the therapeutic options offered to patients. As important however, the new terminology formally acknowledges a common etiology of this disease grouping and opens up the possibility of novel preventive and therapeutic approaches across tissue types.

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KEY POINTS

- Terminology for lower anogenital tract-associated pre-malignant disease historically developed along two separate paths depending on whether the epithelial lesion was mucosal or cutaneous.
- The LAST Project was designed to reassess and harmonize the terminology used to describe human papillomavirus-associated squamous lesions of the lower anogenital tract
- The clarification of this terminology is relevant to clinicians and patients

TABLE 1

LAST Working Groups

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| <p>WG1. Historical review of lower anogenital track HPV-associated squamous lesion terminology.</p> <p>WG2. Squamous intraepithelial lesions. Sub grouped as:</p> <ul style="list-style-type: none">a. Cervix and vaginab. Vulva, penis and scrotumc. Anal canal and perianus <p>WG3. Superficially invasive squamous cell carcinoma.</p> <p>WG4. Biomarkers in HPV-associated lower anogenital squamous lesions.</p> <p>WG5. Implications and implementation of standardized terminology.</p> |
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TABLE 2

Summary of Recommendations

SQUAMOUS INTRAEPITHELIAL LESIONS (Work Group 2)

1. A unified histopathologic nomenclature with a single set of diagnostic terms is recommended for all HPV-associated preinvasive squamous lesions of the LAT.
2. A 2-tiered nomenclature is recommended for noninvasive HPV-associated squamous proliferations of the LAT, which may be further qualified with the appropriate -IN terminology.
3. The recommended terminology for HPV-associated squamous lesions of the LAT is LSIL and HSIL, which may be further classified by the applicable -IN sub-categorization.

SUPERFICIALLY INVASIVE SQUAMOUS CELL CARCINOMA (Work Group 3)

1. The term superficially invasive squamous cell carcinoma (SISCCA) is recommended for minimally invasive SCC of the LAT that has been completely excised and is potentially amenable to conservative surgical therapy.
2. For cases of invasive squamous carcinoma with positive biopsy/resection margins, the pathology report should state whether:
 - The examined invasive tumor exceeds the dimensions for a SISCCA (defined below)
 - OR
 - The examined invasive tumor component is less than or equal to the dimensions for a SISCCA and conclude that the tumor is "At least a superficially invasive squamous carcinoma."
3. In cases of SISCCA, the following parameters should be included in the pathology report:
 - The presence or absence of LVI.
 - The presence, number, and size of independent multifocal carcinomas (after excluding the possibility of a single carcinoma).
4. CERVIX: SISCCA of the cervix is defined as an invasive squamous carcinoma that:
 - Is not a grossly visible lesion, AND
 - Has an invasive depth of 3 mm from the basement membrane of the point of origin, AND
 - Has a horizontal spread of 7 mm in maximal extent, AND
 - Has been completely excised.
5. VAGINA: No recommendation is offered for early invasive squamous carcinoma of the vagina. Owing to the rarity of primary SCC of the vagina, there are insufficient data to define early invasive squamous carcinoma in the vagina.
6. ANAL CANAL: The suggested definition of superficially invasive squamous cell carcinoma of the anal canal is an invasive squamous carcinoma that:
 - Has an invasive depth of 3 mm from the basement membrane of the point of origin,
 - AND
 - Has a horizontal spread of 7 mm in maximal extent, AND
 - Has been completely excised.
7. VULVA: Vulvar SISCCA is defined as an AJCC T1a (FIGO IA) vulvar cancer. No change in the current definition of T1a vulvar cancer is recommended.
8. PENIS: Penile SISCCA is defined as an AJCC T1a. No change in the current definition of T1a penile cancer is recommended.
9. SCROTUM: No recommendation is offered for early invasive squamous carcinoma of the scrotum.
10. PERIANUS: The suggested definition for SISCCA of the perianus is an invasive squamous carcinoma that:
 - Has an invasive depth of 3 mm from the basement membrane of the point of

origin, AND

Has a horizontal spread of 7 mm in maximal extent, AND

Has been completely excised.

BIOMARKERS IN HPV-ASSOCIATED LOWER ANOGENITAL SQUAMOUS LESIONS (Work Group 4)

1. p16 IHC is recommended when the H&E morphologic differential diagnosis is between precancer (-IN 2 or -IN 3) and a mimic of precancer (e.g., processes known to be not related to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cutting).

2. If the pathologist is entertaining an H&E morphologic interpretation of -IN 2 (under the old terminology, which is a biologically equivocal lesion falling between the morphologic changes of HPV infection [low-grade lesion] and precancer), p16 IHC is recommended to help clarify the situation. Strong and diffuse block-positive p16 results support a categorization of precancer. Negative or non block-positive staining strongly favors an interpretation of low-grade disease or a non HPV-associated pathology.

3. p16 is recommended for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (-IN 2 or -IN 3).

4. WG4 recommends against the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, -IN 1, and -IN 3.

SPECIAL CIRCUMSTANCE: p16 IHC is recommended as an adjunct to morphologic assessment for biopsy specimens interpreted as -IN 1 that are at high risk for missed high-grade disease, which is defined as a prior cytologic interpretation of HSIL, ASC-H, ASC-US/HPV-16+, or AGC (NOS).