**Introduction: History of the terminology of lower anogenital tract lesions.**

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The history of terminology for lower anogenital tract (LAT)-associated precancer has developed along two separate paths depending on whether the epithelial lesion is mucosal or cutaneous. Terminology of mucosal cervical, vaginal, and anal lesions was largely developed by general pathologists, gynecologic pathologists, and gynecologists. In contrast, Terminology for cutaneous vulvar, penile, and perianal lesions was largely developed by dermatologists and dermatopathologists. The terminology evolved over a span of 120 years as understanding of disease process increased and treatment advanced. Because treatment of cervical precancer most closely paralleled these changes in terminology, this historical review focuses on the development of cervical precancer terminology and the relationship of terminology to management of cervical lesions. A full review of the history of terminology of all LAT-precancer and early superficial invasive cancer can be found in Darragh et al. J Low Genit Tract Dis. 2012;16(3):205-242. 1 Arch Pathol Lab Med. 2012 Oct;136(10):1266-97

**Mucosal Terminology Cervix: Preinvasive Lesions.**

Sir John Williams first described “intraepithelial precancer” in 1888, but it was not until description of cells that “morphologically looked like cancer but had not invaded below the basement membrane” as carcinoma in situ (CIS)3-5 that treatment was increasingly tailored to terminology. The word “carcinoma” in CIS fostered a 2-tiered clinical approach of hysterectomy for women with CIS and no treatment for women without it (see Figure 1). By the early 1950s, a variety of confusing terms were developed for surface lesions that had less risk of progressing to cancer than CIS. In 1953 terms such as “anaplasia” and “atypical hyperplasia” were replaced by “dysplasia,” which Reagan graded as mild, moderate, or severe.6 Despite the acknowledgement that severe dysplasia and CIS were difficult to differentiate, women with CIS continued being treated by hysterectomy, while women with severe dysplasia were more often treated by cold knife conization.

The term “koilocyte”, from the Greek word for “empty space,” was first used in 1956 by Koss and Durfee to describe cells with ballooned cytoplasm, and in 1976 was linked by Meisels to human papillomavirus (HPV).7,8 The similarity of koilocytotic atypia (KA) with mild dysplasia had previously been noted by many and the link with HPV was the first recognition that HPV had a role in at least low-grade dysplastic changes. However, 7 years prior to Meisel’s discovery, Richart proposed that cervical carcinogenesis was a continuum of disease ranging from mild dysplasia to cervical cancer 9,10 and proposed the term cervical intraepithelial neoplasia (CIN) to emphasize its association as a precursor to cancer. CIN was subdivided into three grades; CIN1, corresponding to mild dysplasia, CIN2 to moderate dysplasia and CIN3 to severe dysplasia. By eliminating the arbitrary division of dysplasia and CIS, the tradition of hysterectomy for the latter and cone for severe dysplasia was slowly replaced by therapy based on the belief that all grades of CIN were on a continuum to cancer, and therefore, all grades of CIN required treatment based on the size and location of the lesion. Hospital-based surgical treatment of precancer was gradually replaced by in-office ablative treatment methods (first cryotherapy, later, CO2 laser ablation). The hospital setting remained the location for managing CIN3/CIS (cold knife conization). Tradition and lingering misunderstanding of the precancerous nature of CIS resulted in a slow demise of this term, which is still often listed as a co-diagnosis with CIN3, i.e. CIN3/CIS.

By the late 1980s, the oncogenic role of HPV was increasingly accepted and the subjectivity of the differentiation between CIN 2 and...
CIN 3 more apparent. This led to numerous proposals to replace the 3-tiered CIN system with a 2-tiered system of low- and high-grade intraepithelial lesion (LSIL and HSIL) similar to the cytologic terminology of the 1988 Bethesda System. However, the promotion of a 2-tiered terminology for histology in the 1990s lacked official support by any professional organizations and was never widely adopted. The 2001 and 2006 ASCCP Consensus Guidelines for the clinical management of cervical histological abnormalities use a 2-tiered terminology for cervix (CIN1 and CIN2,3), except in adolescents and young women with CIN 2 and CIN 3. This exception in the ASCCP Consensus Guidelines perpetuated the clinical reliance on a 3-tiered terminology for cervical histology for managing adolescents and young women.

In the 1990s two important changes occurred in the management of CIN: expectant management of CIN 1, and in-office excision of high-grade precancer (CIN 2, 3) using the loop electrosurgical excision procedure (LEEP); the former secondary to a better understanding of the transience of most CIN 1 lesions and the latter to improved excisional technology that could be performed safely in an office setting (see Figure 1).

In the last decade there has been renewed debate about adopting a 2-tiered low-grade and high-grade terminology for all LAT HPV-associated lesions. The primary concern regarding adopting a 2-tiered system for the cervical histology is that guidelines for management of CIN 2, 3 in adolescents and young women promoted expectant management of CIN 2 with the option to follow lesions reported as CIN 2, 3 but not CIN 3. The counter arguments advanced for adopting a 2-tiered system include that it better reflects the known biology of HPV-associated disease, that diagnostic variability is reduced, and that management based on further divisions in terminology does improve patient outcomes.

Cervix: Early Invasive Lesions
Mestwerdt, in 1947, was first to define microcarcinoma as a carcinoma with invasion no more than 5 mm in depth. Several other terms have been used, including microinvasive carcinoma, early invasive carcinoma, very small carcinoma, early invasive preclinical carcinoma, pin-point invasion, and stage IA cervical carcinoma. The International Federation of Gynecology and Obstetrics (FIGO) changed the definition of stage IA microinvasive carcinoma 6 times between 1961 and 1985, varying treatment recommendations from conization alone, to radical hysterectomy with pelvic lymphadenectomy. Marked interobserver variability in diagnosing microinvasion continues to be of concern.

History of terminology of other Mucosal Areas of the LAT
Early descriptions of precancer of the vaginal and anal canal used the term carcinoma in situ to describe full thickness intraepithelial changes. By the 1980s gynecologic pathologists began to adopt the language of intraepithelial neoplasia that had been adopted for cervix in describing vaginal intraepithelial neoplasia (VaIN) and anal intraepithelial neoplasia (AIN), with similar grading applied.

History of terminology of Cutaneous Lesions of the LAT
Cutaneous HPV-associated precancers on the vulva, perianus, and penis were all initially named after the two clinicians who first described them; Louis Queyrat, in 1911, described glans penis intraepithelial lesions (erythroplasia of Queyrat) and JT Bowen, in 1912, described intraepithelial lesions on the shaft of the penis, buttocks and thighs (Bowen disease). Bowen’s disease eventually became the term applied to cutaneous precancers throughout the LAT, especially by dermatologists.

References
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28 Sulzberger MB, Sartenstein DL. Epithroplasia of Queyrat. AMA Arch Derm Syphilol 1933;28:798-806.
Figure 1.
Changes to the terminology and number of tiers used to describe cervical precancer over time with corresponding management options (procedure). See text for additional details. CKC, cold knife conization; Cryo, cryotherapy; RX, treatment. Modified with permission. Courtesy of T.M. Darragh and J.T. Cox.
Why the Findings of the LAST (Lower Anogenital Squamous Terminology) Conference Matter to You

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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 these organs may take one of two possible pathways. One that supports virion production but which may or may not lead to the development of transient lesions not destined for invasion and termed variably 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 overexpression leads to cell proliferation and clonal expansion of relatively undifferentiated cells by viral replication and the development of the truly pre-malignant lesion that, if left untreated, can become an invasive cancer. These processes are similar across tissue types and 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 developed to describe this pathologic and clinical spectrum of disease for the purpose of patient management. The history of this terminology, coming from multiple different disciplines, is described in this Educate the Educators update.

Based on a growing recognition of a need for unified terminology the American Society for Colposcopy and Cervical Pathology and the College of American Pathologist Pathology and Laboratory Quality Center jointly convened a process to address this challenge. This 14 month process brought together 53 experts and opinion leaders from a variety of clinical and scientific disciplines. Five Work Groups (see Table 1) were assembled to conduct systematic reviews of the relevant literature and discussions of the relevant issues, and the process culminated in a consensus conference in March of 2012 and subsequent publication of the findings (J Low Genit Tract Dis. 2012 Jul;16(3):205-42 and Arch Pathol Lab Med. 2012 Oct;136(10):1266-97).

Table 1: LAST Work Groups

1. Historical review of lower anogenital track HPV-associated squamous lesion terminology.
2. Squamous intraepithelial lesions. Sub grouped as:
   a. Cervix and vagina
   b. Vulva, penis and scrotum
   c. Anal canal and perianus
5. Implications and implementation of standardized terminology.

This can be further qualified using the –IN terminology to facilitate clinical management. Immunohistochemistry with p16 testing is recommended when a diagnosis of –IN2, using the older terminology is made, or to help adjudicate cases of disagreement about diagnosis between pathologists. A strong diffuse positive staining pattern is consistent with a HSIL diagnosis, while negative staining supports a 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, invades stroma ≤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.

The clarification of this terminology is not simply an esoteric exercise but instead is relevant to clinicians and patients alike. The historic heterogeneity of clinical and histopathologic terminology has lead 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 future 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.
Molecular Markers for LAST Recommendations

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HPV is well-recognized as a necessary but not sufficient cause of cervical carcinomas and dysplasias. As such, molecular markers for HPV have been increasingly used as an aid in the evaluation and diagnosis of clinically relevant cervical squamous dysplasias. Several different markers and methodologies are discussed in the literature but the quality and clinical relevance of these studies vary widely. As part of the LAST Recommendation preparations, one of the working groups performed a comprehensive literature search that identified 2,291 articles from which 72 high-quality articles were selected for data extraction. These articles were selected based on inclusion criteria targeting clinical validation studies with established sensitivity, specificity and performance against an adjudicated histologic standard, and studies evaluating at least 100 samples. Cytology studies using three-way adjudication and histology as a gold standard were also included. Of the 72 articles, 53 addressed p16 which was identified as the only marker with sufficient data to allow full analysis of its utility in the evaluation of lower anogenital tract lesions. ProExC and Ki67 showed similar trending data to p16 but there were insufficient data available for independent analyses. The majority of the articles addressed cervical squamous lesions but a subset evaluating vulvar/penile and anal sites showed similar results to the cervix, supporting the applicability of the final recommendations across all anogenital sites.

In depth analysis of the selected high quality articles showed that the data support the use of p16 immunohistochemistry (IHC) in specific situations when evaluating squamous lesions of the anogenital tract. The currently available evidence did not support the use of IHC markers in combination with other markers. The final recommendations and the supporting literature, consisting of 18 articles, were independently evaluated by the LAST recommendation outcomes analysis collaborators. The term “recommend” was used if the recommendations are unlikely to change based on further evidence. Overall, the quality of the evidence supporting improved diagnostic reproducibility with hematoxylin and eosin (H&E) /p16 was rated as high and the evidence supporting improved sensitivity of H&E/p16 for the diagnosis of a precancer lesion, high-moderate.

Final recommendations regarding use of p16 IHC include:

1. The use of p16 IHC when the H&E morphologic differential diagnosis is between HSIL (-IN2 or -IN3) and a mimic such as immature squamous metaplasia, atrophy, reparative changes, and other similar benign findings.

2. The use of p16 IHC when the lesion shows morphologic features of -IN2 which is a biologically equivocal lesion. Strong and diffuse block positive p16 results would support classification of the lesion as HSIL (-IN2) while negative or non-block positive results strongly favor LSIL (-IN1) or a non-HPV associated process. However, p16 should not be used when the morphologic differential diagnosis is between LSIL (-IN1) and negative since -IN1 is often p16 negative. Given the poor reproducibility of the diagnosis of -IN2, this recommendation is targeted at improving diagnostic accuracy of a single pathologist’s interpretation of HSIL vs. LSIL.

3. The use of p16 IHC as an adjudication tool when there is lack of pathology consensus in the diagnosis of HSIL (-IN2 or -IN3) and LSIL (-IN1). Various studies have shown that the use of p16 substantially improves interobserver variability in the interpretation of lower anogenital tract squamous lesions.

4. In cases where the morphology is unequivocally negative or diagnostic of LSIL (-IN1) or HSIL (-IN3), p16 IHC should not be routinely used. This specific recommendation is to discourage overuse of p16 IHC and misinterpretation of cases based on p16 results. At this time, there is insufficient data in the literature to indicate that the natural history of p16 positive morphologically unequivocal –IN1 differs from p16 negative –IN1, although there is some evidence to suggest that it represents a higher risk lesion. p16 IHC is positive in the vast majority of CIN3 (>99%) which argues against its utility in cases with morphologically unequivocal –IN3.

4a. In the special circumstance where a patient with a prior cytologic diagnosis of HSIL, ASC-H, AGC-
NOS or ASC-US/HPV16+ has a biopsy where a precancer lesion is not identified, the use of p16 IHC is recommended as an adjunct to H&E morphology. These patients are at high-risk for missed high-grade disease and p16 IHC can help to draw attention to small lesions. The p16 positive area must also meet morphologic criteria for a diagnosis of precancer before issuing a diagnosis of HSIL (-IN2 or -IN3).

These recommendations represent the first step in standardizing biomarker use in evaluating lower anogenital squamous lesions. Further studies will be required to address unanswered questions such as: 1) the natural history of p16-positive LSIL and whether these patients should be managed differently than those with p16-negative LSIL, 2) potential overutilization of p16 IHC and impact on patient management, and 3) the utility of markers other than p16 IHC whether used singly or in combination.
Superficially Invasive Squamous Cell Carcinoma (SISCCA)

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LAST has recommended that the term “superficially invasive squamous cell carcinoma” (SISCCA) be used to clearly identify a minimally invasive squamous cell carcinoma of the lower anogenital tract that has been completely excised and is potentially amenable to conservative surgical therapy. All health care professionals now have this common term for early invasive squamous carcinomas that can be managed by local excision only. Through the adoption of SISCCA for each genital site, comparison of management results for an identical stage disease is possible, and any confusion in defining early invasive disease across body sites can potentially be eliminated. Since the risk of metastasis differs across body sites, each anogenital site has a unique definition of SISCCA. The primary determinants of SISCCA at each site are depth and width of invasion. Additional parameters may be used some sites. The definitions of SISCCA of the cervix and vulva are based upon a wealth of high quality data and analyses available in published literature. In contrast, the definitions of SISCCA of the perianal and anal canal sites have been recommended with expert opinion due to limited data. Given its rarity, SISCCA is not used for the vagina. The definition of SISCCA for each site of the lower genital tract in women is shown in Table 2.

The determination of resection margin status is best determined from a single marked or painted surgical biopsy. In the cervix, for example, this will usually mean a LEEP or cone specimen. Invasive carcinoma can be defined in punch biopsies, but the size of these specimens is usually suboptimal to definitively identify SISCCA. If multiple specimens have been taken from a lesion the final diagnosis must be based on the composite findings in all the specimens. In all cases of SISCCA the presence or absence of lymphovascular space involvement (LVI) should be noted, even though this feature is not a defining feature of SISCCA. If multifocal independent carcinomas are present, their number and size should be noted.

LAST did not favor retention of the term “microinvasive carcinoma” of the cervix for several reasons. Even though tumor volume is the major predictor of nodal metastases, the current definition of “microinvasive carcinoma” does not use lateral spread as a criterion. Secondly, SISCCA of the cervix is an invasive squamous carcinoma that:

- Is not a grossly visible lesion, AND
- Has an invasive depth of 3 mm or less from the basement membrane of origin, AND
- Has a horizontal spread of 7 mm or less in maximal extent, AND
- Has been completely excised.

NOTE: SISCCA of the cervix is equivalent to a FIGO IA1 cervical carcinoma

SISCCA of the vulva is an invasive carcinoma that:

- Is a lesion 2 cm or less in size, AND
- Is confined to the vulva and perineum, AND
- Has stromal invasion of 1 mm or less, as measure from the epithelial-stromal junction of the adjacent superficial dermal papilla.

NOTE: SISCCA of the vulva is equivalent to a FIGO T1A vulvar carcinoma

Table 2 — Definitions of Superficially Invasive Squamous Cell Carcinoma (SISCCA) of the Lower Genital Tract in Women

- SISCCA of the anal canal is an invasive carcinoma that:
  - Has an invasive depth of 3 mm or less from the basement membrane of the point of origin, AND
  - Has a horizontal spread of 7 mm or less in maximal extent, AND
  - Has been completely excised.

- SISCCA of the perianus, the region within 5 cm. from the anal verge, is an invasive carcinoma that:
  - Has an invasive depth of 3 mm or less from the basement membrane of the point of origin, AND
  - Has a horizontal spread of 7 mm or less in maximal extent, AND
  - Has been completely excised.

- SISCCA of the vagina — Insufficient data to define a vaginal SISCCA
the presence of LVI as an independent prognostic factor in cervical carcinoma continues to be unresolved, although it is used as an exclusion criterion for “microinvasive carcinoma”. In the current definition of “microinvasion” there is ambiguity regarding what constitutes complete excision of the lesion. Also, continued use of “microinvasive carcinoma” limits international comparability of management results.

Consistent terminology should be used in surgical pathology reports of invasive squamous carcinomas that have positive resection margins. In these cases it is important to indicate whether the current biopsy could quality as a SISCCA and be amenable to local treatment only, or whether more advanced disease is already evident. The terminology for the reporting of early invasive squamous carcinomas of the lower genital tract in women needs to refer to SISCCA terminology. The pathology report should state: 1) Whether the invasive tumor exceeds the dimensions for a SISCCA (see Table 2) OR 2) Whether the examined invasive tumor is less than or equal to the dimensions for a SISCCA and conclude that the tumor is “At least a superficially invasive squamous carcinoma.”

SIL (CIN) may be present at margins of SISCCA of the cervix. A risk of persistent or recurrent disease exists in women with either negative margins or margins involved with SIL, although women in the latter group are at increased risk for both persistent SIL and invasive disease. Management of women with cervical SISCCA with SIL at a resection margin could be followed expectantly or undergo re-excision.

In summary, the LAST unifying term, SISCCA, for minimally invasive squamous carcinomas of the lower genital tract will permit consistent identification of women with invasive squamous carcinoma who can be offered conservative local therapy.
For the production and distribution of the 2011 Educate the Educators program, ASCCP received unrestricted education grants in 2008-09 from the following corporations:

Merck & Company, Inc.
Roche Diagnostics Corporation
Hologic, Inc.
Qiagen
MTM Laboratories

ASCCP acknowledges the support of these corporations. ASCCP also states that all decisions relating to the following development and production activities were made independent of any commercial interest: identification of learning needs and determination of objectives; selection and presentation of content; selection of all persons in a position to control content; selection of the educational method; and, evaluation of the activity.