Title
Why LAST? Polishing the Gold Standard

Journal
AJSP Review and Reports, 18(4)

ISSN
2381-5949

Authors
Darragh, Teresa M
Wilbur, David C

Publication Date
2013

DOI
10.1097/pcr.0b013e3182990d77

Peer reviewed

Why LAST? Polishing the Gold Standard

Teresa M. Darragh, MD, and David C. Wilbur, MD,†*

Abstract: Pathologic diagnoses are often considered the gold standard, the truth on which many clinical management decisions are based. Yet, morphologic interpretations are inherently subjective and may result in significant diagnostic error and interobserver variability. Mixed with the plethora of potentially confusing medical terms that have been applied to human papillomavirus–associated squamous lesions of the lower anogenital tract, miscommunication and potential patient harm may ensue. Mirroring the Bethesda System for gynecologic cytology, the Lower Anogenital Tract Squamous Terminology (LAST) Project, jointly sponsored by the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology, recognizes both the strengths and limitations of histopathologic diagnoses. Based on our current understanding of human papillomavirus–associated infection and precancer, the LAST Project recommends a 2-tiered terminology for squamous intraepithelial lesions and couples it with the judicious use of the biomarker, p16, to enhance diagnostic accuracy. The LAST Project also recommends a united approach to superficially invasive squamous carcinomas of the lower anogenital tract, emphasizing their potential amenability to conservative therapy. Adoption of the LAST Project's recommendations, in essence, polishes the gold standard: improving diagnostic precision, communication between pathologists and our clinical colleagues, and, ultimately, patient care.

Key Words: terminology, squamous intraepithelial lesion, human papillomavirus, superficially invasive squamous cell carcinoma, p16

(*Pathol Case Rev* 2013;18: 152–153)

COMMENTARY

Many consider pathologic diagnoses to be the gold standard. Indeed, numerous clinical management decisions are based specifically on the tissue diagnoses rendered by pathologists. Unfortunately, in some situations, this gold standard may not be as golden as was previously assumed. Morphologic interpretations are open to subjectivity, and perhaps even more problematic, the terminology used to convey these diagnoses has been highly variable, confusing, and, in some cases, misleading. The practice of pathology couples the art of visual interpretation with the science of medicine. As we continue to strive to practice evidence-based medicine, having reliable and reproducible histopathologic diagnoses, based on our best science, and using clear, concise, consistent, relevant, and well-defined terms are essential. The Lower Anogenital Tract Squamous Terminology (LAST) Project, jointly sponsored by the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology, brings these issues to the forefront as they relate to human papillomavirus (HPV)–associated squamous lesions of the lower anogenital tract and acknowledges both the strengths and limitations of histopathologic diagnoses.[1–3]

Historically, cervical intraepithelial neoplasia (CIN) and its counterparts at other anogenital sites have been portrayed as a morphologic spectrum—our pathology texts are riddled with cartoons and patchwork photomicrographs depicting this continuum—a schema that arbitrarily splits a presumed continuous progression of disease into 3 diagnostic categories. The dividing line between these categories is not a sharp line, however; rather, it is a hazy zone prone to significant interpretive variability and hence lack of reproducibility. In addition, substantial diagnostic variation is observed when distinguishing true disease from variations of normal—when we are making our most educated guesses as to the underlying nature of the process. Can we do better in providing accurate, clearly communicated, and relevant diagnoses to our clinical colleagues? The answer is yes.

In addition to the subjective lack of reproducibility and inaccurate reflection of current biologic reality, many of the terms that pathologists have used to describe HPV-associated intraepithelial disease have different significance depending on the specific anatomic site, the clinical specialty or the subspecialty of the pathologist, or historical convention. These issues also extend to the terminology and criteria used to define the concept of early invasive carcinoma (that is, microinvasion). The LAST Project addresses this important topic as well. It synthesizes the multiplicity of terms and criteria used to define early invasive squamous cell carcinoma across lower anogenital tract sites. Under the rubric of superficially invasive squamous cell carcinoma, this new term unites a highly important category of lesions emphasizing their potential amenability to conservative therapy.

In the not so distant past, the treatments and management options for HPV-associated diseases of the anogenital tract were limited, and hence, clear and refined terminology was not as vital. Because essentially all HPV-associated cervical lesions were treated in our efforts to reduce the number of women who developed cervical cancer, the clinical consequences of diagnostic variation were minimal. And it worked! Cervical cancer rates in the United States have dropped dramatically in the last 50 some years through our screening efforts and aggressive attempts to eradicate these lesions. Yet, we have learned much about the biology of HPV and its associated diseases in recent decades—including identifying it as the cause of cervical cancer. Short of invasive disease, we now recognize 2 broad morphologic manifestations of HPV on squamous epithelia, which are identical across the entire lower anogenital tract: one is

From the *UCSF, Departments of Pathology and Obstetrics, Gynecology & Reproductive Sciences, San Francisco, CA; and †Harvard Medical School, Massachusetts General Hospital, Department of Pathology, Boston, MA.

Reprints: Teresa M. Darragh, MD, UCSF Mt Zion Medical Center, 1600 Divisadero, Room B618, San Francisco, CA 94115.
E-mail: Teresa.darragh@ucsf.edu.

The LAST Project was jointly funded by the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology.

D.C.W. is a shareholder (<$10,000) in Merck. T.M.D. receives research supplies for anal cytology from Hologic and honorarium for webinar on anal cancer screening; she is on the advisory board of and has stock options in OncoHealth.

ISSN: 1082-9784
DOI: 10.1097/PCR.0b013e3182990d77

typically a relatively ubiquitous, self-limited, transient viral infection, and the second is the less common lesion that is a potential precancer.

Guided by this increased understanding of HPV biology and balancing the benefits of treatment with its potential harms, our clinical approach, particularly for cervical disease, has morphed into a dichotomous one. Treatment is reserved for patients with potential precancers, whereas patients with HPV infection are kept under surveillance, allowing for spontaneous resolution of the vast majority. It makes sense to match our current understanding of the science of HPV infection and its clinical manifestations with our histopathologic terminology and lump, rather than split, the squamous intraepithelial lesions into low-grade infections and high-grade potential cancer precursors.

This is not really a new idea. As far back as 1990, Dr Richart,[4] who coined the CIN system about 20 years earlier, proposed a 2-tiered modification to the CIN terminology. Major pathology texts have used this dichotomous approach for years. The LAST Project synthesizes our current knowledge and recommends clear, concise, consistent, and relevant terminology based on our best science. The recommendations extend the use of a 2-tiered nomenclature to include all HPV-associated lesions of the lower anogenital tract—cervical or vaginal or vulvar or anal or perianal—thereby reducing the confusion caused by the plethora of terms used to describe these same pathologic entities that have been based on body site, gender, or historical convention—usage that has varied over time, from laboratory to laboratory, and medical specialty to medical specialty.

In the ideal world, we would have a magic marker that would indicate that a specific high-grade lesion would progress to invasive disease if not treated. We are not there yet—the science has not yet progressed to this level of specificity. But pathologists have many tools that can help meld the more objective science of medicine and pathology with its long practiced subjective visual art. Currently, our best tool for assessing the overall risk of HPV-associated lesions is the p16 immunostain. Although not specific to precancers caused by HPV, in the appropriate context of a morphologically suspicious lesion of squamous epithelium of the lower anogenital tract, a diffuse or "block-positive" p16 immunostain indicates that an oncogenic version of the virus has started the process of neoplastic transformation with alteration of the cell cycle—changes that are necessary for progression to malignancy. This biomarker helps objectify our "best guesstimate" in cases presenting difficult morphologic patterns such as the differential between high-grade squamous intraepithelial lesion and morphologic mimics such as atrophy or immature metaplasia with exuberant reactive changes. Biomarkers can reduce the educated guesswork of our diagnostic challenges and increase their reproducibility among pathologists. Using p16, individual pathologists are better able to classify difficult or controversial cases and achieve diagnostic reproducibility with similar accuracy as a panel of experts.

As recommended by the LAST Project, a 2-tiered nomenclature for squamous intraepithelial lesions, indications for the appropriate use of biomarkers, and a united approach to superficially invasive squamous carcinomas can make our histopathologic diagnoses more reproducible, reliable, and accurate. It inserts more science, objectivity, and consistency into our communication with clinical colleagues. Use of the LAST recommendations will lead to overall improved patient management and ultimately better patient care, bringing greater luster to our newly polished gold standard.

REFERENCES

1. Darragh TM, Colgan TJ, Thomas Cox J, et al., for Members of the LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology [published online ahead of print June 28, 2012]. *Arch Pathol Lab Med* 2012;136(10):1266–1297.
2. Darragh TM, Colgan TJ, Thomas Cox J, et al., for Members of the LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis* 2012;16(3):205–242.
3. Darragh TM, Colgan TJ, Thomas Cox J, et al., for Members of the LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Int J Gynecol Pathol* 2013;32(1):76–115.
4. Richart RM. A modified terminology for cervical intraepithelial neoplasia. *Obstet Gynecol* 1990;75(1):131–133.