Stratification of Vulval Carcinoma and its Precursors

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Royal Infirmary of Edinburgh and Edinburgh Cancer Research Centre, Edinburgh, UK
# WHO Classification of tumours of the vulva

<table>
<thead>
<tr>
<th>Epithelial tumours</th>
<th>Neuroectodermal tumour</th>
<th>Soft tissue tumours</th>
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<tr>
<td>Squamous cell tumours and precursors</td>
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Outline

- HPV-associated neoplasia
- The LAST recommendations
- Vulval disease
  - Usual-type VIN (SIL) and associated carcinomas
  - Differentiated type VIN and associated carcinomas
  - HPV and non-HPV-related disease
HPV and Squamous Neoplasia

HPV Infection → De-regulation of E6/E7 (p16 positive)

Normal → Low Grade SIL

HPV Infection → Telomerase Activation
Inhibition of Apoptosis
Genetic Changes
Immune Response
Smoking

Low Grade SIL → Invasive Cancer
High Grade SIL → Invasive Cancer
Human Papillomavirus Infection and Anogenital Disease

- HPV infection is present in 99.7% of invasive cervical carcinomas
- Mucosal HPV infection can also cause vulval and vaginal precancerous lesions and genital warts
Molecular Organisation

Doorbar J Clin Sci 2006;110:525-41
The Papillomavirus Life Cycle

Doorbar J Clin Sci 2006;110:525-41
Checkpoints

CDK4/CDK6 → CycDs → pRb → pRb

p16 p18 p15 p27 p21 → p53

CDK2 → CycE → DNA Replication (S phase)

Cdc25

CDK2 → CycA → Mitosis (M phase)

Cdc2 → CycB
HPV and Neoplastic Progression

Modified from Doorbar J Clin Sci 2006;110:525-41
What Governs Progression?

Â HPV type
  ï High-risk HPV types, particularly 16 and 18

Â Persistence of HPV infection

Â Up-regulation of E6/E7

Â Loss of capacity to replicate viral DNA

Â HPV integration
  ï Chromosome sites random
  ï Viral breakpoint consistent (E1/E2)
Summary

- High vs low-risk HPV types
- HPV 16 dominates neoplastic vulval disease
- Productive vs transforming infection
- Up-regulation of E6/E7 expression key
- Associated with HPV integration
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The LAST Project

Slides courtesy of Dr Mark Stoler and Dr Teresa Darragh
Recommendation

There is evidence of biological and morphological similarity of HPV-related squamous lesions across the lower anogenital tract so nomenclature should be harmonised.

Non-HPV-related squamous lesions should have a separate distinctive nomenclature e.g. differentiated VIN in the vulva.
There is a unified HPV-related biology

Å Vulva

Å Penis
There is a unified HPV-related biology

Male – Perianal

Cervix
Lesions are p16 positive in all sites
Recommendation

• A 2-tiered nomenclature is recommended for non-invasive HPV-associated squamous proliferations of the lower anogenital tract

• This may be further qualified with the appropriate –IN terminology e.g. CIN, VaIN, VIN etc

• Rationale

  • WG4 could find no molecular marker-based studies to support 3-tiered biology.

  • WG4 found that the use of p16 to potentially upgrade or downgrade equivocal (CIN2) lesions effectively leads to a 2-tiered classification system.

  • A 2-tier system is more reproducible
The recommended terminology for HPV-associated squamous lesions of the LAT is *low grade squamous intraepithelial lesion* (LSIL) and *high grade squamous intraepithelial lesion* (HSIL), which may be further classified by the applicable –IN subcategorization.
Biomarkers evaluated after 1st tier review

- p16
- Ki67 (Mib1)
- ProExC
- HPV L1 protein
- HPV 16/18 mRNA
- Telomerase (TERC)
- HPV genotyping
Recommendation

• p16 IHC is recommended when the H&E morphological differential diagnosis is between precancer (IN 2 or IN 3) and a mimic of precancer (e.g., immature squamous metaplasia, atrophy, reparative epithelial changes).

• Strong and diffuse block-positive p16 results support a categorization of precancerous disease.
Increasing Cancer Risk

**p16 IHC**

- **HSIL vs. Mimic**
- **Negative**

**LAST Terminology**

**Histological Interpretation**

**High-Grade SIL**

**Treatment**

**Follow-up**

**Clinical Management**
Recommendation Notes

Åp16 should not be used if the H&E morphological differential diagnosis is between low-grade disease (LSIL/CIN 1) and negative, as LSIL can be either p16 negative or positive.

Åp16 IHC is not recommended if the pathologist’s histological diagnosis is “obvious” LSIL/CIN1.
Recommendation

Åp16 IHC should not be used as a routine adjunct to histological assessment of biopsy specimens with morphological interpretations of negative, LSIL (–IN 1), and HSIL (–IN 3)

ÅExcept for cases interpreted as ≤–IN 1 that are at high risk for missed high-grade disease
References: The LAST Project

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.


International Journal of Gynecological Pathology 2013; 32(1): 76-115
Journal of Lower genital Tract Disease 2012; 16(3): 205-242
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  - Transitional cell carcinoma 8120/3

## Neuroectodermal Tumour
- Ewing sarcoma 9364/3

## Soft Tissue Tumours
- Benign tumours
  - Lipoma 8850/0
  - Fibroepithelial stromal polyp
  - Superficial angiomyxoma 8841/0
  - Superficial myofibroblastoma 8825/0
  - Cellular angiofibroma 9160/0
  - Angiomyofibroblastoma 8826/0
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    - Dermatofibrosarcoma protuberans 8832/1
ISSVD Classification of VIN, 2004

Å VIN, usual type
  • VIN, warty type
  • VIN, basaloid type
  • VIN, mixed (warty/basaloid) type

Å VIN, differentiated type

Å VIN, unclassified type