The Clinical Significance of Stratifying Vulval Squamous Carcinoma into HPV and Non-HPV Related Variants
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<table>
<thead>
<tr>
<th></th>
<th>HPV</th>
<th>Non-HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Fourth to sixth decade</td>
<td>Sixth to ninth decade</td>
</tr>
<tr>
<td>Etiology</td>
<td>Oncogenic viral infection</td>
<td>Chronic inflammation (lichen sclerosis)</td>
</tr>
<tr>
<td>Precursor</td>
<td>HSIL (VIN3), usual type</td>
<td>dVIN</td>
</tr>
<tr>
<td>Biomarker expression</td>
<td>p16 overexpression</td>
<td>Abnormal p53 expression</td>
</tr>
<tr>
<td>Outcome</td>
<td>Favorable</td>
<td>Less favorable (more likely to have nodal mets, recur locally)</td>
</tr>
</tbody>
</table>

Vulvar squamous cell carcinoma
- Two pathways: HPV-associated and HPV-independent

HPV-associated vulvar squamous cell carcinoma
- Younger age
- Better prognosis (?)
- Associated in situ component more commonly identified
- More often multifocal involvement
- Strong association with previous cervical cytology abnormalities
- Cigarette smoking is a risk factor

HPV-associated vulvar squamous cell carcinoma
- HSIL (VIN3) a.k.a. usual high-grade VIN
- Invasive squamous cell carcinoma (basaloid or warty type)
**HPV-INDEPENDENT VULVAR CA**

First detailed description of differentiated or simplex VIN was in 2000 (Yang and Hart, AJSP)

Only a handful of reported cases that have progressed to invasive ca

**THEREFORE** – natural history of non-HPV vulvar ca is not well described and our ability to detect it early (i.e. at a pre-invasive stage) is doubtful

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**dVIN (per Yang and Hart criteria)**

1. epidermal hyperplasia with parakeratosis and elongated and anastomosing rete ridges,
2. significant basal cytological atypia
3. (mentioned cells with abundant eosinophilic cytoplasm)
Molecular abnormalities in dVIN

- p53 mutation in most cases
- p53 shows either:
  - increased (basal) expression compared to adjacent benign squamous epithelium – can be subtle
  - complete loss of p53
Conclusions

p53 overexpression in dVIN is subtle, and difficult or impossible to distinguish from normal pattern unless A. there is marked atypia, or B. there is adjacent normal epithelium for comparison.

Therefore of limited use in small biopsies.
**dVIN vs HSIL (VIN3): Progression Free Survival**

**Table 3**: Cases with discrepant p16 IHC and HPV PCR results

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>VIN</th>
<th>Inv SCC</th>
<th>p16</th>
<th>HPV PCR</th>
<th>HPV in situ</th>
<th>Other information</th>
<th>Final HPV classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>dVIN</td>
<td>M/WK</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>HPV-Independent</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>dVIN</td>
<td>M/WK</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>HPV-Independent</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>HSIL</td>
<td>Basalid</td>
<td>-</td>
<td>-</td>
<td>Prov. CIN</td>
<td></td>
<td>HPV-Associated</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>dVIN</td>
<td>M/WK</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>HPV-Independent</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>NCR</td>
<td>M/WK</td>
<td>-</td>
<td>-</td>
<td>F</td>
<td></td>
<td>HPV-SCC/Positive</td>
</tr>
</tbody>
</table>

Conclusions

- Morphology leads to incorrect assessment of HPV status in 15-20% of cases.
- p16 IHC: sensitivity of 100% and specificity of 98.4%.
- HPV PCR and HPV ISH can give false positive results/false negative results.

Recommended approach to assessment of HPV status

- Clinical information (age, results of cervical cytology), morphology, and p16 IHC taken into account in determining HPV status (with p16 accorded more weight than the other variables).
- HPV PCR or HPV ISH can be used in cases that are indeterminate based on clinical/histopathological/p16 results.

HPV-independent VIN is more aggressive than HPV-associated VIN.

What about invasive VSCC?

Prognostic Significance of HPV Status

- Prognostic worse prognosis for HPV-negative tumours.
- Ansink Gynecol Oncol 1994
- Monk Obstet Gynecol 1995
- van de Nieuwenhof Cancer Epidemiol Biomarkers Prev 2005
- Lindell Gynecol Oncol 2010
- Dong AJSP 2015
- *See Gynecol Oncol 2016
- Hay J Low Genit Tract Dis 2016
- *Allo, Clarke, unpublished
- McAlpine Histopathol 2017, in press

- Not prognostic
- Pinto Gynecol Oncol 2004
- Santos AJSP 2006
- Alonso Gynecol Oncol 2011

p16 and Outcome in VSCC

Survival by p16 Status and Surgical Era

In multivariable analysis, prognostic effect independent of age and stage. McAlpine Histopathol 2017.
Invasive VSCC in BC

- 122 HPV-independent and 79 HPV-associated invasive VSCC
- Median age: 75 yrs and 58 yrs, respectively
- HPV status a prognostic factor for overall survival, disease specific survival, and relapse free survival (p=0.0004, p<0.0001, and p=0.023, respectively)
- In multivariable analysis HPV status is the most significant prognostic factor

VAAD

1. marked acanthosis with variable verruciform architecture,
2. loss of the granular cell layer with superficial epithelial cell pallor, and
3. plaque like layers of parakeratosis.

NB – can coexist with dVIN

HPV-independent vulvar squamous cell carcinoma (alternate pathway!)

VAAD (vulvar acanthosis with altered differentiation) or DEVIL

Verrucous carcinoma
Conclusions

- Invasive VSCC is 2/3 HPV-independent and 1/3 HPV-associated
- VIN is >90% HPV-associated
- HPV-independent VIN and VSCC have a worse prognosis than their HPV-associated counterparts
- There appears to be an alternate HPV-independent pathway that is unrelated to p53
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