

## The Pathology of Penile Tumours

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## Penile cancer teams in UK

- 12 centres for penile cancer work (10 in England and Wales, 2 in Scotland)
- Incidence of penile cancer in UK is 1-2/100,000 per year (approx 600 new cases)
- Recommended that each team serves at least 4 million population with 25 cases minimum
- Organ sparing techniques with reconstruction more widely available (radical and partial penectomy performed less often)



## Penile cancer teams

- Inguinal sentinel lymph node surgery introduced
- Use of megablocks for interpretation of anatomical boundaries
- Annual meeting in London for penile cancer histopathologists/clinicians
- EQA
- RCPATH dataset (2<sup>nd</sup> edition in production 2013)



## Common variants

- Usual type squamous carcinoma
- Basaloid [aggressive]
- Sarcomatoid [aggressive]
- Warty
- Warty-basaloid



## Basaloid squamous carcinoma

- Aggressive high grade tumour
- 50% have nodal mets at the time of presentation
- Flat/ulcerated tumour with endophytic growth pattern
- Basaloid cells +/- abrupt necrosis/keratinisation
- Comedo necrosis may be seen
- Associated with HPV 16 and 18, but not BXO
- Vascular invasion often present
- Poor prognosis
- May be associated with a basaloid type of carcinoma in situ
- May metastasise to distant sites without inguinal lymph node involvement



## Basaloid squamous carcinoma penis

Can be papillary in architecture, closely resembling high grade urothelial carcinoma



## Uncommon/rare variants

- Verrucous carcinoma
- Mixed verrucous/usual
- Papillary carcinoma
- Pseudohyperplastic carcinoma\* [good prognosis]
- Carcinoma cuniculatum [good prognosis]
- Adenosquamous carcinoma
- Pseudoglandular (acantholytic) carcinoma [aggressive]
- Clear cell carcinoma\* [aggressive]
- Mixed tumours

\*typically foreskin location



## Classic Verrucous carcinoma

- Always well differentiated
- Associated with verruciform hyperplasias
- Associated with lichen sclerosis in 60% cases
- Slowly growing
- May be multifocal and recur locally
- Exophytic or burrowing invasion (broad based papillae without fibrovascular cores – ‘Elephants feet’)
- Koilocytosis/Viral changes not seen
- Do not metastasise to lymph nodes
- Good prognosis unless mixed with more poorly differentiated tumour

[courtesy Dr C Corbisley]



## ‘Verruciform’ tumours

- Verrucous carcinoma
- Warty carcinoma
- Papillary carcinoma
- Carcinoma cuniculatum

[all may have a component of exophytic cauliflower-like growth pattern with papillomatosis, hyperkeratosis and acanthosis]



Penile carcinoma is thought to follow 2 etiologic pathways;

- HPV infection
- other factors including balanitis xerotica obliterans/lichen sclerosis



## Variants associated with HPV

- Basaloid
- Warty
- Warty-basaloid
- [Some usual type (<50%)]
- Clear cell carcinoma

[overall HPV is found in approx 50% of all penile carcinomas]



## HPV and oncogenesis

Site	% squamous carcinomas with high risk HPV
Cervix	~ 100%
Vagina	~ 90%
Vulva	~ 50%
Anus	80-90%
Penis	40-50%
Oropharynx	25% (esp non smokers)



## Use of p16 in Penile SCC

- Number of studies looking at the use of p16 immunohistochemistry in penile SCC
- There is a preferential association of p16 positivity with basaloid morphological features
- Consistently negative in verrucous, papillary, pseudohyperplastic, cuniculatum and pseudoglandular penile carcinomas



## Use of p16 in penile SCC

- All studies provide evidence that p16 expression can be used as a marker of HPV infection in penile cases
- Useful in the differential diagnosis of penile SCC subtypes
- However significance of HPV infection in prognosis of penile SCC is controversial due to insufficient data



- Although there are a few studies that indicate p16 may represent a promising prognostic biomarker, others show no survival difference.
- Prognosis more likely dictated by histological grade, depth of invasion and nodal status than by subtype or HPV status



## Variants not associated with HPV

- Verrucous
- Papillary
- Pseudohyperplastic
- Cuniculatum
- [Some usual type (>50%)]

[some of these non-HPV related cases are postulated to be related to lichen sclerosis/balanitis xerotica obliterans (BXO)]



## Mixed tumours and other types

- Up to 25% of tumours may show more than one pattern
- Focal high grade areas may co-exist within low grade tumours, including verrucous tumours, making adequate sampling mandatory



## Other primary tumours

- Malignant melanoma
- Sarcomas
- Epithelioid haemangioma



## Risk stratification for carcinoma

- Tumour type/grade
- Stage
- Lymphovascular invasion
- Perineural invasion



## Penile carcinoma – TNM classification (7<sup>th</sup> edition, 2009)

- pTis: carcinoma in situ
- [pTa: non-invasive verrucous carcinoma]
- pT1: Tumour invades subepithelial connective tissue
  - pT1a: Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated
  - pT1b: Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated or undifferentiated
- pT2= Tumour invades corpus spongiosum or cavernosum
- pT3 = Tumour invades urethra
- pT4 = tumour invades other adjacent structures



**Histologic grade in penile squamous carcinoma: visual estimation versus digital measurement of proportions of grades, adverse prognosis with any proportion of grade 3 and correlation of a Gleason-like system with nodal metastases** Chaux A et al. Am J Surg Pathol 2009;33:1042-1048.

- Grade 1 reserved for tumours composed entirely of cells indistinguishable from normal except for minimal basal/parabasal atypia
- Grade 3 = tumour with any proportion of anaplastic cells



## Precancerous lesions

- Squamous carcinoma in situ, ['undifferentiated PeIN']
  - basaloid, warty or warty-basaloid
- Differentiated PeIN (recently described for penile lesions, around 2010). Frequently associated with BXO and with some good prognosis variants e.g. papillary carcinoma
- [?Dysplasia]



## Differentiated PeIN

- Acanthosis with hyperkeratosis, parakeratosis and hypergranulosis
- Elongated anastomosing rete ridges
- Subtle abnormal maturation (enlarged keratinocytes with abundant eosinophilic cytoplasm)
- Keratin pearl formation
- Dysplastic hyperchromatic basal cells
- Absent koilocytes (not associated with HPV; p16 negative)
- >50% cases have associated BXO
- Mucosal surface of foreskin predominant; older men predominate



## Differential diagnosis of differentiated PeIN

- Squamous hyperplasia
- Pseudohyperplastic carcinoma



## Undifferentiated PeIN

- Basaloid, warty or warty-basaloid
- Population of small to intermediate sized cells in basaloid type, round to ovoid nuclei and high n/c ratio. Usually marked nuclear pleomorphism in warty-basaloid subtype
- Koilocytosis prominent in warty and warty-basaloid subtypes
- All strongly HPV associated (p16 positive – should be diffuse, except for the parakeratotic layer)
- Numerous mitotic figures and apoptosis
- Glans location predominant; no strong association with BXO; younger men predominate
- Differential diagnosis = Bowenoid papulosis (young individuals, penile shaft location, multiple regressing lesions clinically)
- Paget's disease (e.g. spread from a urothelial carcinoma) could also enter the differential diagnosis of CIS



## Risk category for nodal metastasis

Hungerhuber E *et al. Urology* 2006;68:621-625

- pT1, grade 1 or grade 2 = low risk
- Grade 3 invasive, any pT = high risk
- Invasive carcinoma not in above groups = intermediate risk
- % cases with inguinal metastases for low, intermediate and high risk were 8%, 29% and 75% respectively
- Inguinal LN dissection recommended for high risk group
- Dynamic sentinel LN biopsy for intermediate risk group
- Surveillance for low risk group



## Sentinel lymph node biopsy

- Hypothesis that there is a stepwise dissemination of metastases in LNs
- Sentinel LN localised using technetium<sup>99</sup> lymphoscintigraphy +/- blue dye
- False negative 'pseudosentinel' LNs can result from blockage of lymphatics in the true positive sentinel LN and re-routing of lymph flow
- High resolution ultrasound and FNAC now recommended prior to sentinel LN procedure to avoid above false negatives (patients with impalpable disease)



## Sentinel LNs for penile cancer

- Slice all nodal tissue thinly at cut-up (2mm slices) and embed all nodal tissue
- 2 cytokeratins done on each block to include high molecular weight forms
- Levels not routine due to thin slicing



## The prognostic index: a useful pathologic guide for prediction of nodal metastases and survival in penile squamous carcinoma

Chaux A *et al. Am J Surg Pathol* 2009;33:1049-57.

- 3 factors combined (histologic grade, anatomical level and presence/absence of perineural invasion) to give a score between 2 and 7
- Score 2-3 = low risk (0% nodal metastasis in 193 patients)
- Score 4 = intermediate risk (20% nodal mets)
- Score 5-7 = high risk (64% nodal mets)
- 5 year survival rates for scores 2-4 = 95%; 65% for scores 5 and 6 and 45% for score 7



## Metastases to penis

- Prostate
- Colon
- Kidney
- Bladder
- Melanoma



## References

Seminars in Diagnostic Pathology 2012 Vol 29  
(entire issue devoted to penile cancer)

