

Tumours of the Penis.

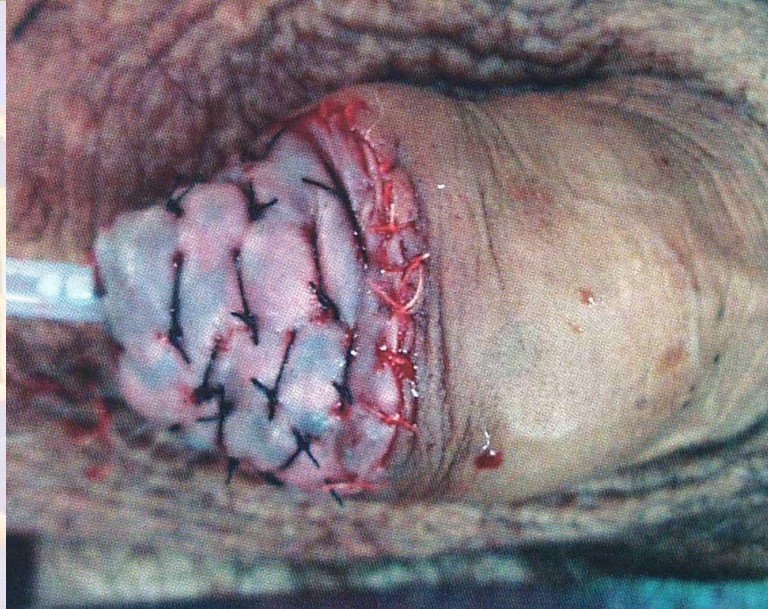
The proposed new WHO classification and outcome of the recent ISUP consultation



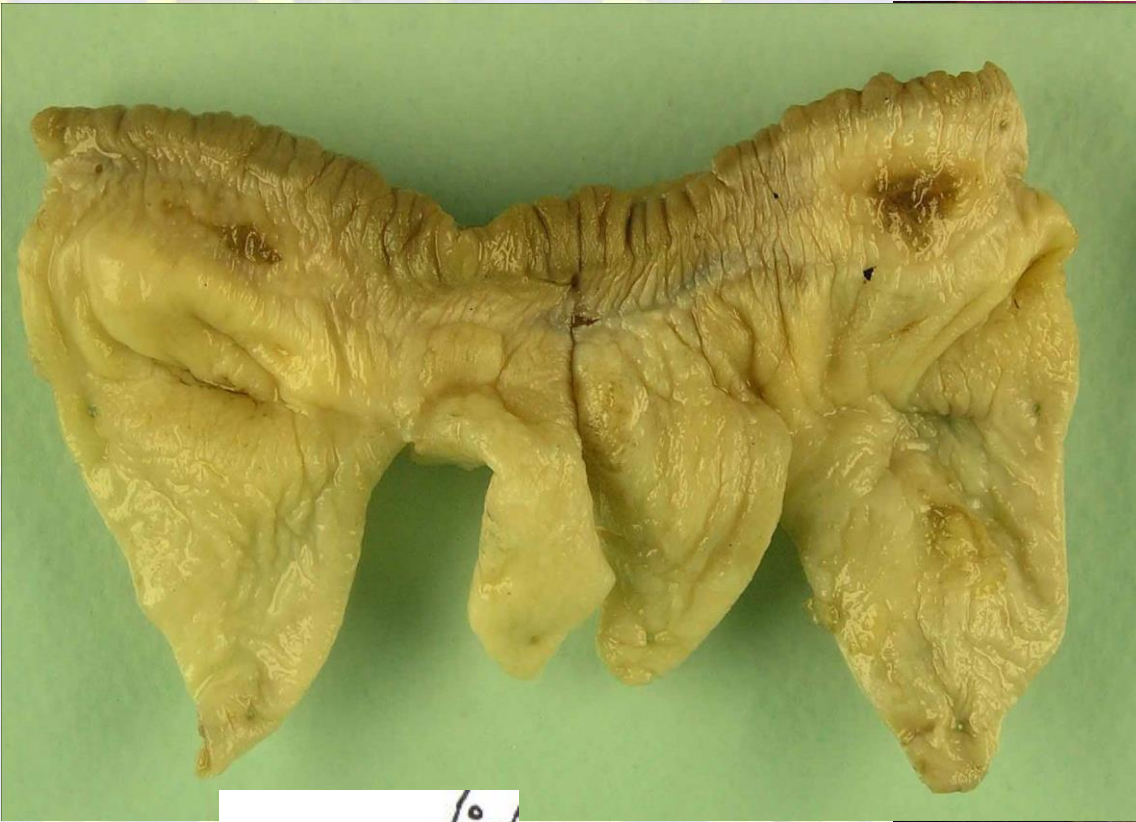
Dr Cathy M Corbishley

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Glansectomy with reconstruction



Glans Resurfacing.



Scope

- The New RCPATH dataset for Penile and Distal Urethral tumours published July 2015
- **ISUP Consultation on Penile Cancer, March 2015, Boston**
 - Penile Intraepithelial neoplasia (PeIN)
 - The new WHO classification (2016)
 - Staging and the new TNM 8 (2016)
- The International Collaboration on Cancer Reporting (ICCR) guidelines on Penile and Distal Urethral tumours

The RCPATH Penile and Distal Urethral dataset

Royal College of Pathologists Standards and datasets for reporting cancers

Dataset for penile and distal urethral cancer histopathology reports

Published online July 2015

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What's new in the RCPATH dataset

- Penile Intraepithelial Neoplasia (PeIN)
- Subtyping and new tumour variants
- New surgical techniques. Glansectomy, sentinel nodes and glans resurfacing
- The addition of a dataset for distal urethral squamous tumours
- Use of modified TNM7 staging using evidence based prognostic indicators
- Diagrams to aid orientation, cut up, staging and margin assessment

ISUP consultation on Penile Tumours, Boston March 2015

- Penile Intraepithelial Neoplasia (PeIN)
 - Elsa Velasquez
- Subtyping and Grading of Penile tumours
 - Antonio Cubilla
- Staging of Penile tumours
 - Cathy Corbishley

All are authors of WHO 2016 and have sent evidence to Mahul Amin for the TNM 8 consultation

New WHO Classification of Penile Intraepithelial neoplasia (2016)

1. Non-HPV-related PeIN
 - Differentiated (simplex) PeIN
2. HPV-related PeIN
 - Basaloid PeIN
 - Warty PeIN
 - Warty-basaloid PeIN
3. Other rare patterns of PeIN
 - Pleomorphic
 - Spindle
 - Clear cell
 - Pagetoid

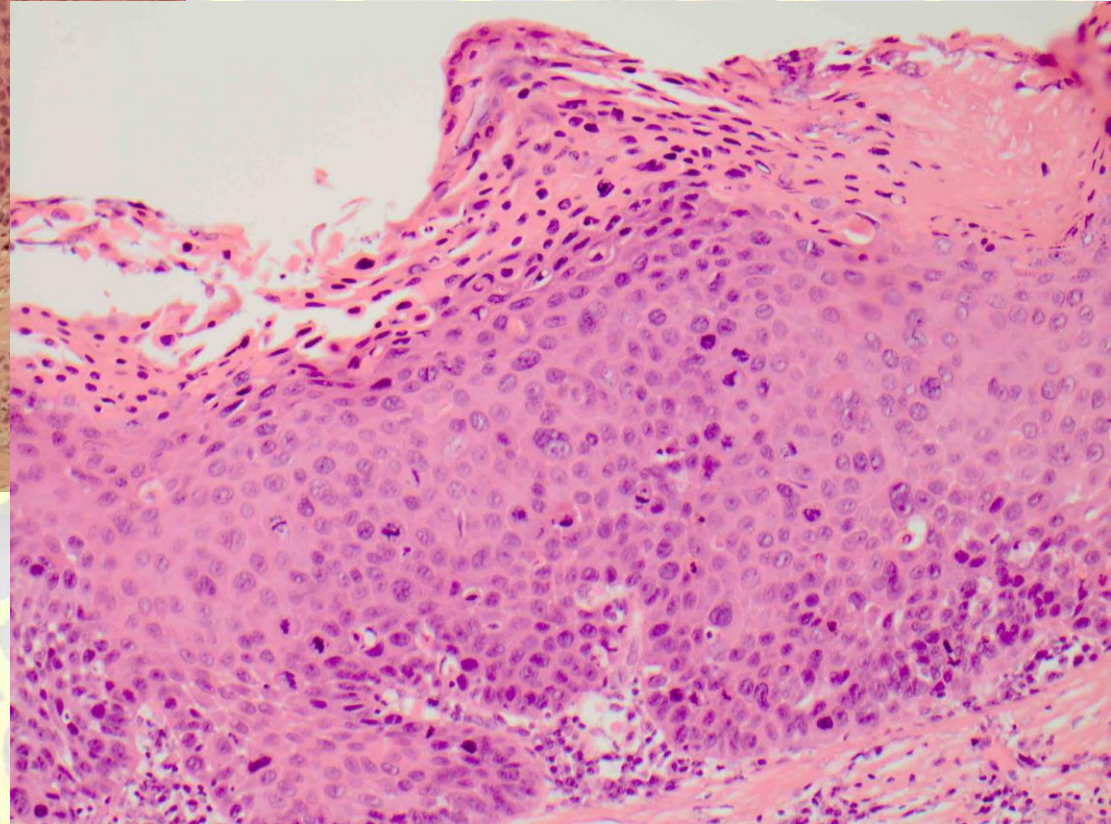
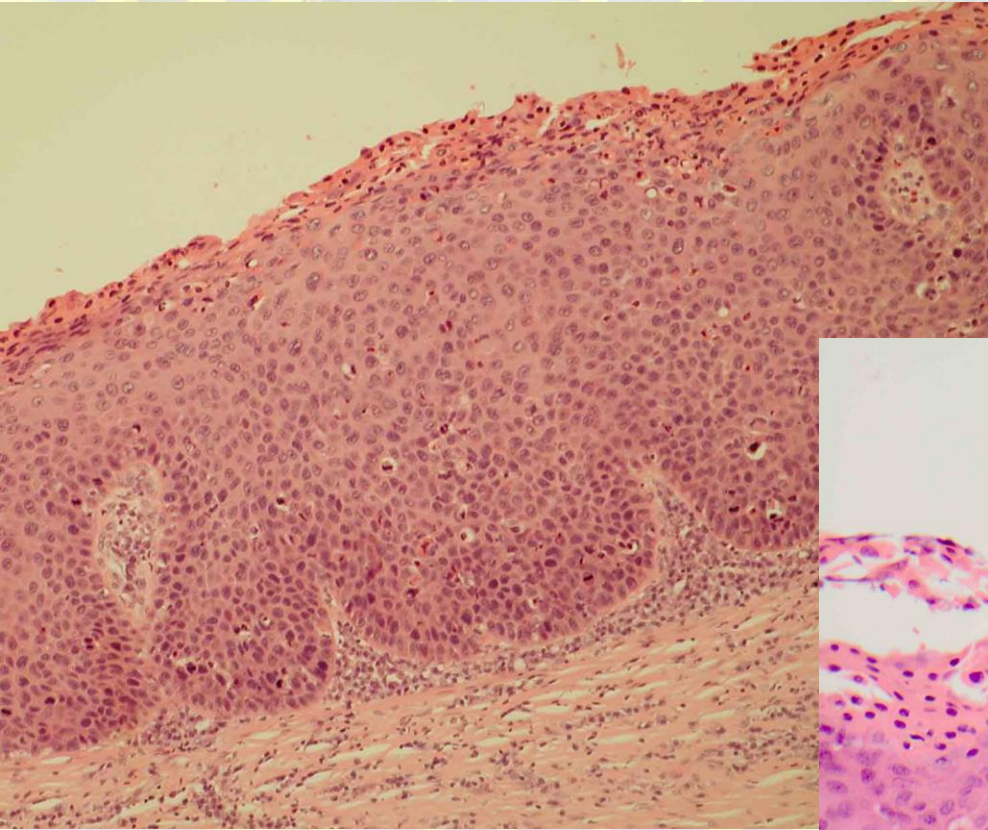
Precursor lesions

1. Undifferentiated PeIN

- Associated with high risk HPV types including 16
- Morphologically often Basaloid/Warty features
- P16 usually positive – may be useful in margin assessment, especially if there is a Pagetoid pattern
- Not associated with Lichen sclerosis
- Associated with Basaloid, Warty and some Usual type Carcinomas

Undifferentiated PeIN

Basaloid and Warty Basaloid

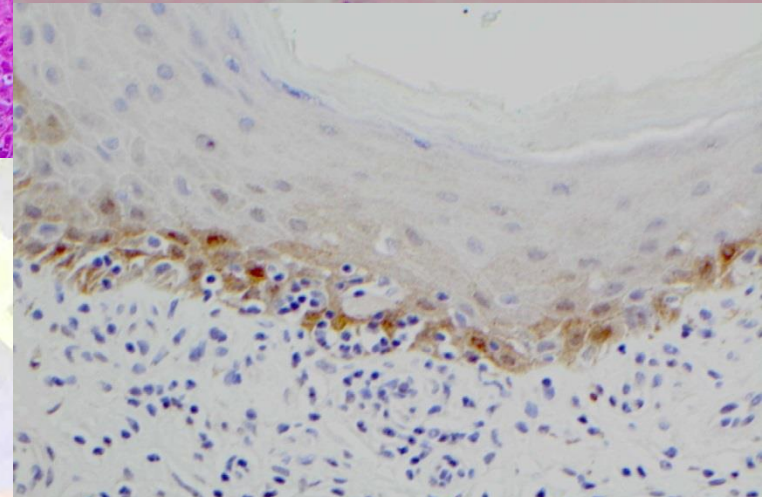
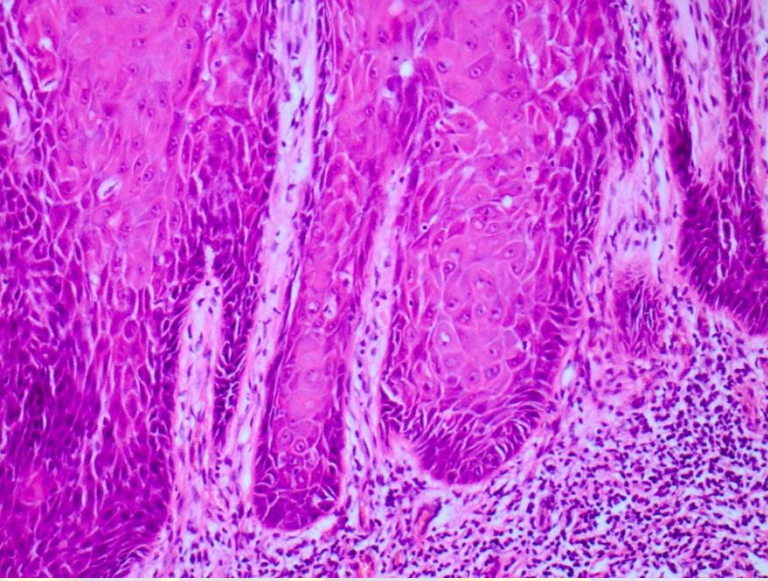
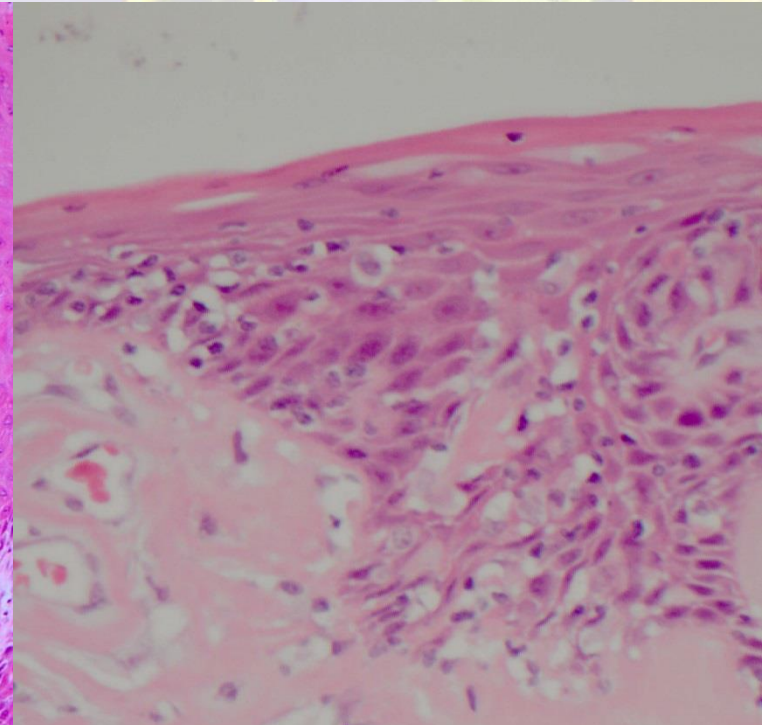
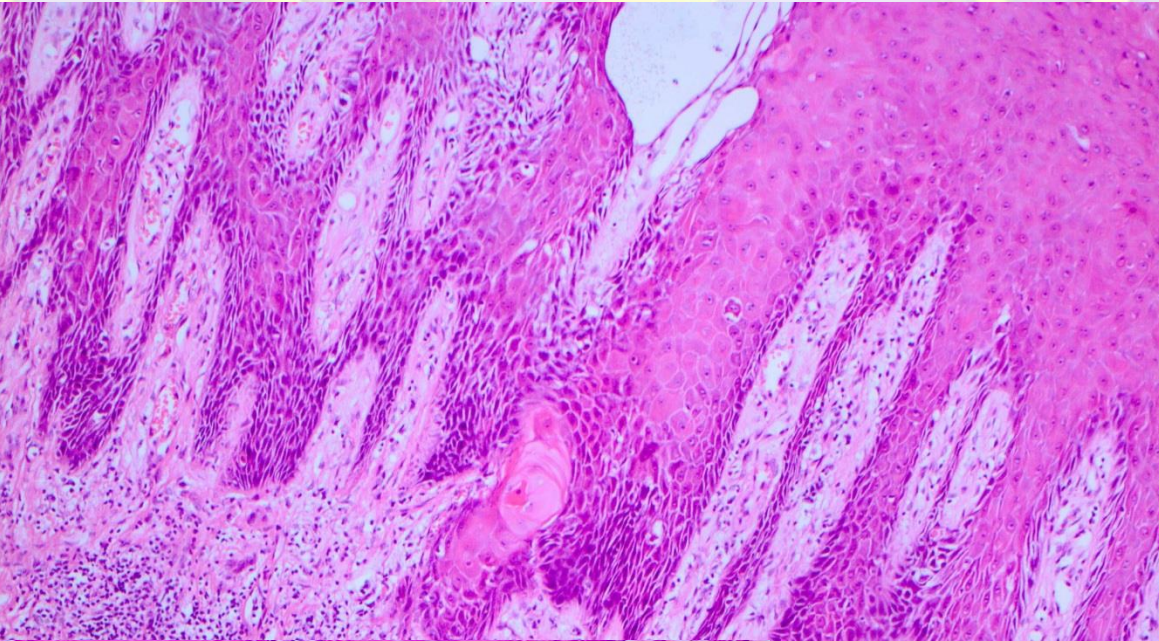


Precursor Lesions

2. Differentiated PeIN

- Clinically flat or slightly raised pale, white or erythematous lesions
- Associated with Lichen sclerosis
- Atypical changes seen in basal layers of the epithelium only
- Associated with architectural atypia, hyperkeratosis and aberrant keratinisation
- P16 and HPV usually negative
- May give rise to Usual type SCCs, Verrucous carcinomas and pseudohyperplastic SCC
- Only recently recognised as an entity
- Sometimes misdiagnosed as atypical lichen planus or not recognised as a significant precursor lesion

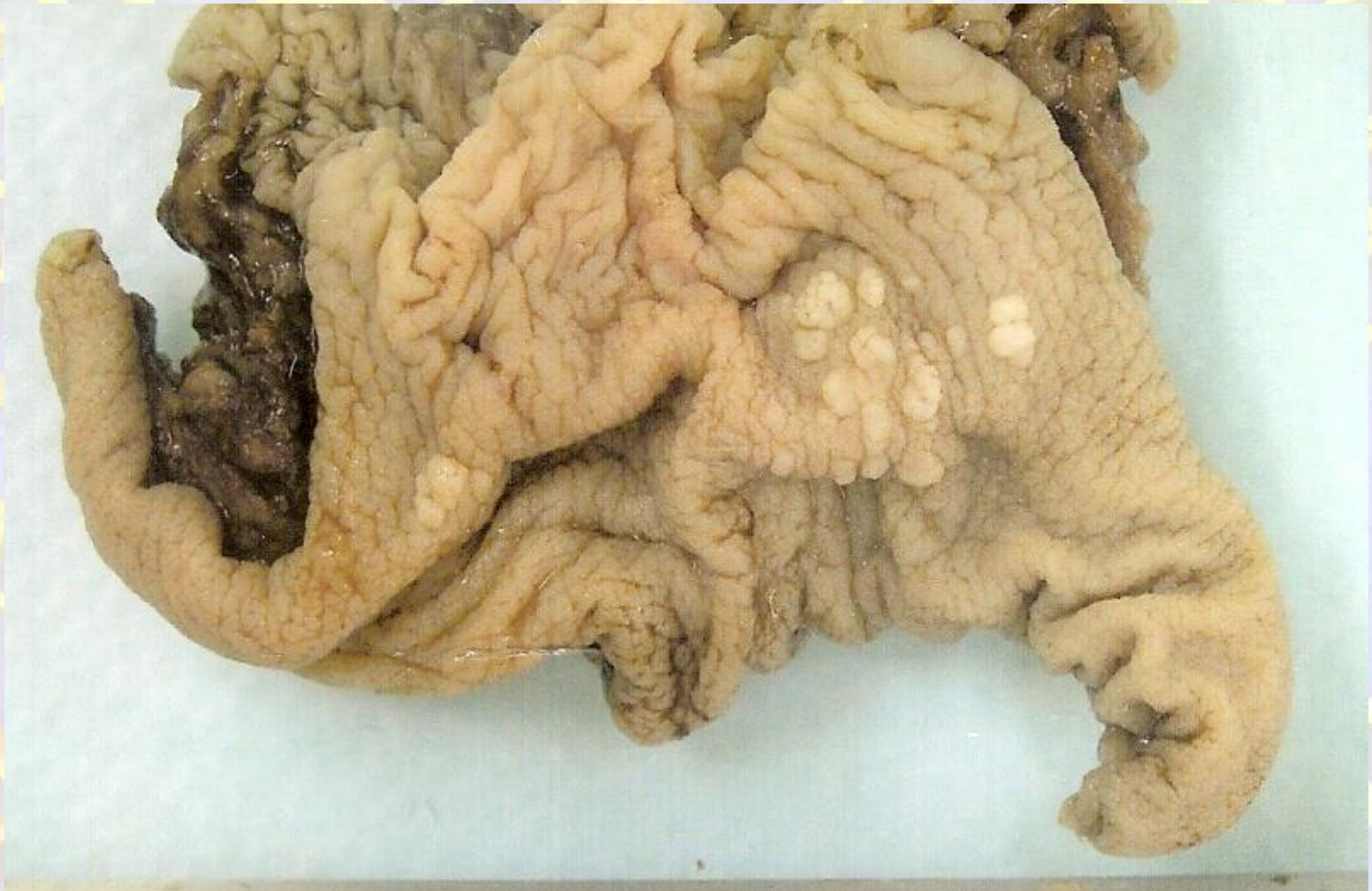
Differentiated PeIN – P16 negative



Bowenoid Papulosis?

- Clinically defined condition – looks like multiple small benign warts
- Usually on **shaft** in young men, less common on foreskin and glans
- Associated with HPV 16
- Histologically identical to warty/basaloid undifferentiated PeIN
- May regress spontaneously or with anti wart treatments
- May possibly progress to neoplasia particularly in immunosuppressed individuals
- **Better to describe as Warty/Basaloid Undifferentiated PeIN and correlate with clinician in the setting of a specialist MDT before making a definitive clinicopathological diagnosis of Bowenoid papulosis**
- **Not covered in new WHO classification**

Multiple warty papules of the foreskin (and shaft) –
could be Bowenoid papulosis



Preneoplastic conditions of the Penis and PeIN terminology

- PeIN terminology should be used in pathology reporting rather than Carcinoma in situ or Dysplasia
- Lesions such as Bowens disease, Bowenoid papulosis and Erythroplasia of Queyrat are clinically, not pathologically, defined lesions and should not be used as diagnostic terms
- **PeIN does not need to be graded and is regarded as high grade by definition (agreed at ISUP/USCAP consensus meeting 2015 and will be in WHO book)**
- There is still a place for diagnosing atypia which falls short of Undifferentiated or Differentiated PeIN to avoid overtreatment and encourage follow up

Penile Cancer main subtypes WHO 2016

Subdivision by HPV status

A. Non-HPV-related penile SCCs

1. SCC

Usual carcinoma

Pseudohyperplastic carcinoma

Pseudoglandular carcinoma

2. Verrucous carcinoma

Pure verrucous carcinoma

Carcinoma cuniculatum

3. Papillary carcinoma, NOS

4. Adenosquamous carcinoma

5. Sarcomatoid squamous carcinoma

6. Mixed carcinoma

B. HPV-related penile SCCs

7. Basaloid carcinoma

Papillary-basaloid carcinoma

8. Warty carcinoma

Warty-basaloid carcinoma

Clear cell carcinoma

9. Lymphoepithelioma-like carcinoma

C. Other rare carcinomas

Commonest sub-types of Squamous Cell Carcinoma of the Glans penis and Foreskin

- Usual type SCC. (up to 70% cases)
- Verrucous Carcinoma (5%)
- Warty SCC (5%)
- Basaloid SCC. (10%)
- Papillary SCC (1-5%)
- Sarcomatoid Squamous cell carcinoma. (1-2%)
- Mixed Tumours. (up to 30%)

Rare subtypes of SCC penis ($<1\%$)

- Pseudohyperplastic Carcinoma
- Carcinoma Cuniculatum (variant of Verrucous carcinoma)
- Clear cell SCC (variant of Warty SCC)
- Pseudoglandular (acantholytic) SCC
- Adenosquamous carcinoma
- Lymphoepithelioma-like SCC

Rare and very rare non squamous tumours of the Penis

- Malignant melanoma (more usually Urethral primary)
- Neuroendocrine Carcinoma and Small Cell carcinoma
- Metastases (Renal Carcinoma, Melanoma, Lymphoma, Prostate, Renal and Bladder carcinoma) – usually within Corpora cavernosa
- Extramammary Paget's disease
Urothelial spread if on glans.
Anogenital/cutaneous (apocrine) type if on scrotum/perineum
- True sarcomas and mesenchymal tumours
- Lymphoreticular tumours

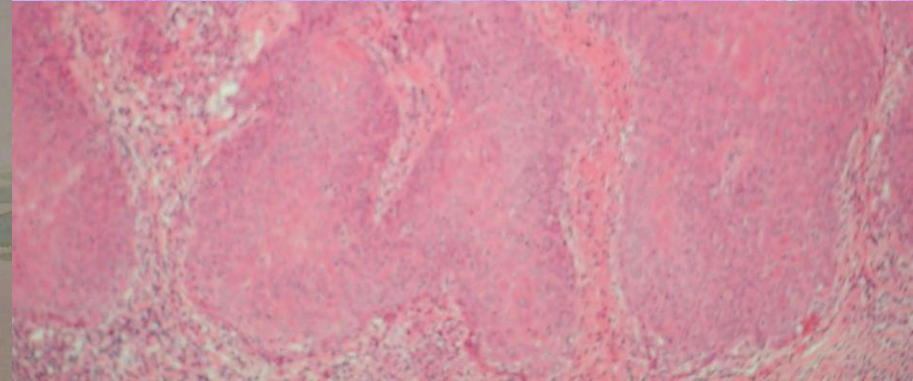
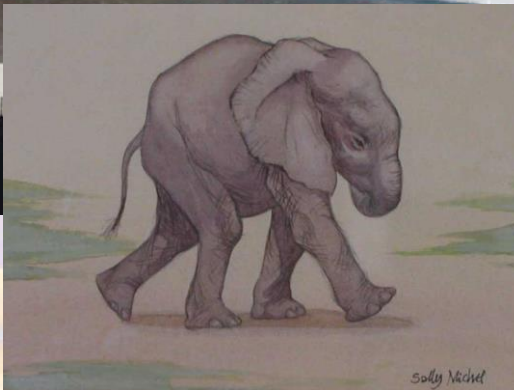
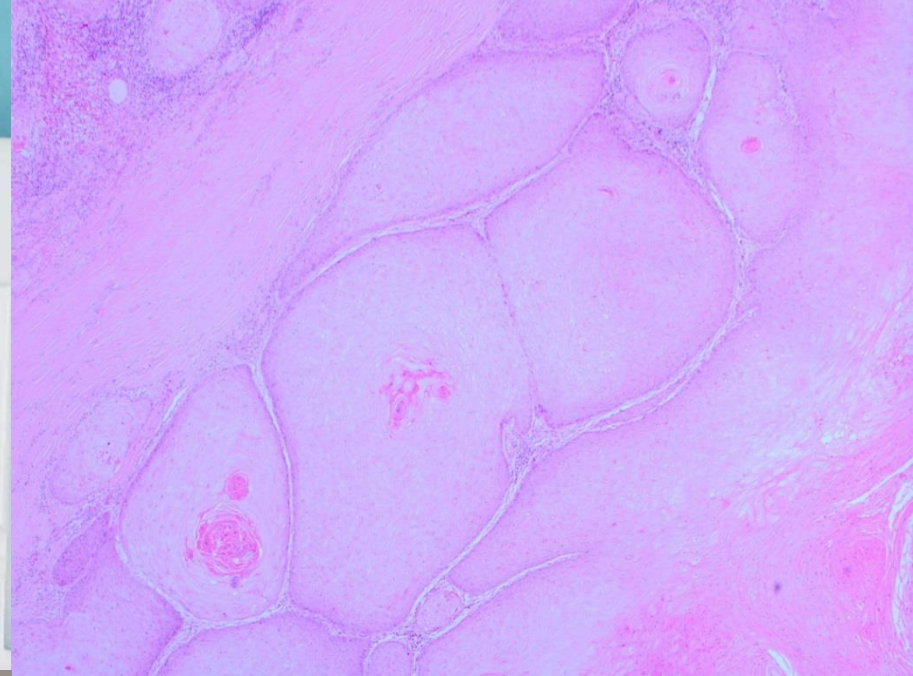
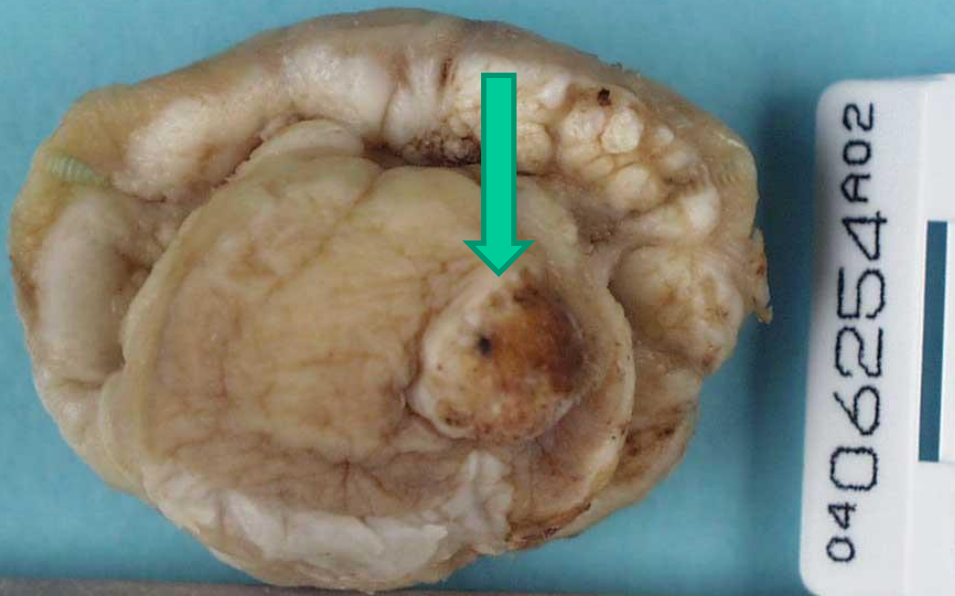
Tumour types associated with
Lichen sclerosis and
Differentiated PeIN but not HPV

- Usual type SCC (80%)
- Verrucous carcinoma and Carcinoma cuniculatum
- Pseudohyperplastic carcinoma

Classic Verrucous carcinoma

- Well differentiated and slow growing
- Associated with LS in at least 60% cases.
- P16 and HPV negative
- Exophytic or burrowing invasion (broad based tumour islands without fibrovascular cores – ‘Elephants feet’)
- May be multifocal and recur locally
- Does not metastasise to lymph nodes
- Good prognosis unless mixed with more poorly differentiated SCC or sarcomatoid tumour
- May be misdiagnosed as benign in small biopsies or incorrectly subtyped by non specialist pathologists
- Carcinoma cuniculatum variant looks similar but with areas of keratin filled cysts and endophytic sinuses

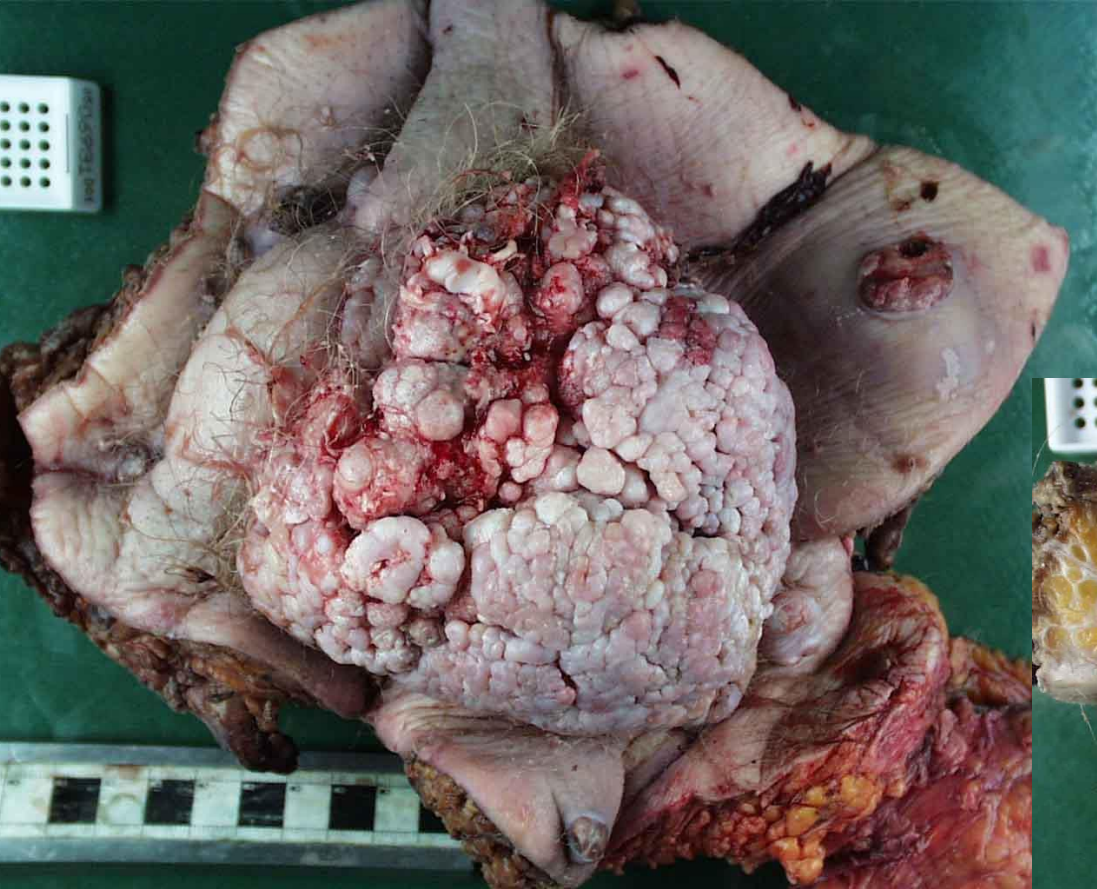
Verrucous Carcinoma associated with Lichen sclerosis



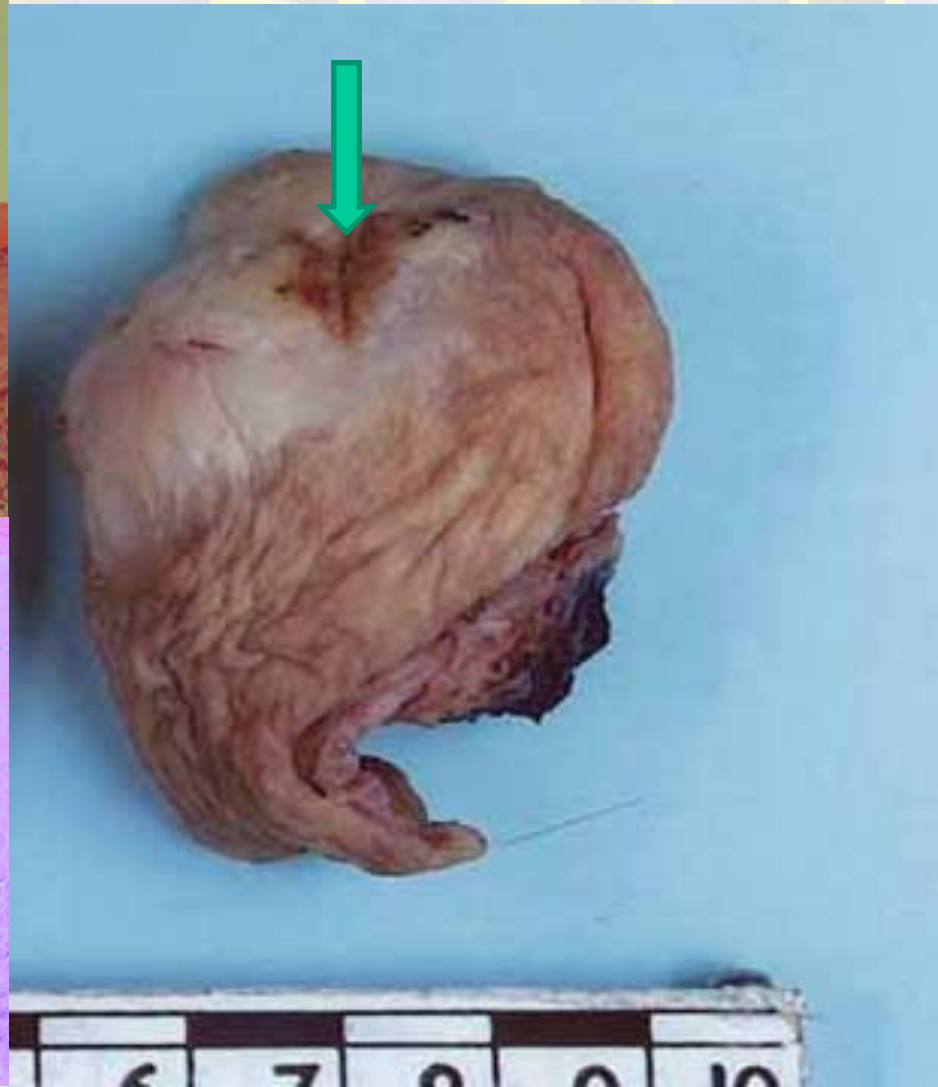
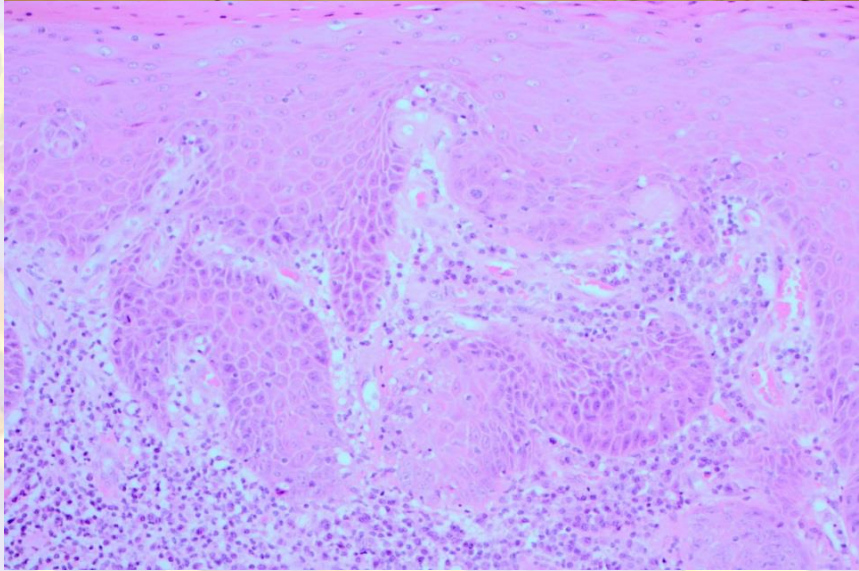
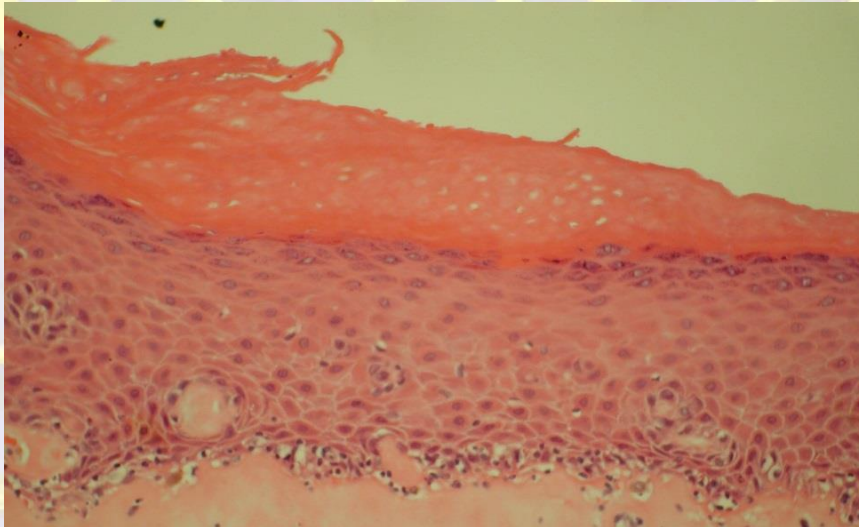
Multifocal Verrucous Carcinoma of Foreskin with precursor lesions on glans



Verrucous Carcinoma – an extreme longstanding case



Glanssectomy showing LS, differentiated PEIN and pseudohyperplastic SCC)



Tumour types associated with HPV and Undifferentiated PeIN

- Warty SCC
 - Warty basaloid SCC
 - Clear cell SCC (p63 and HMW keratin positive)
- Basaloid SCC
 - Papillary basaloid SCC
- Lymphoepithelioma-like SCC
- Usual type SCC (20%)
- **HPV and/or P16 staining not necessary for diagnosis**

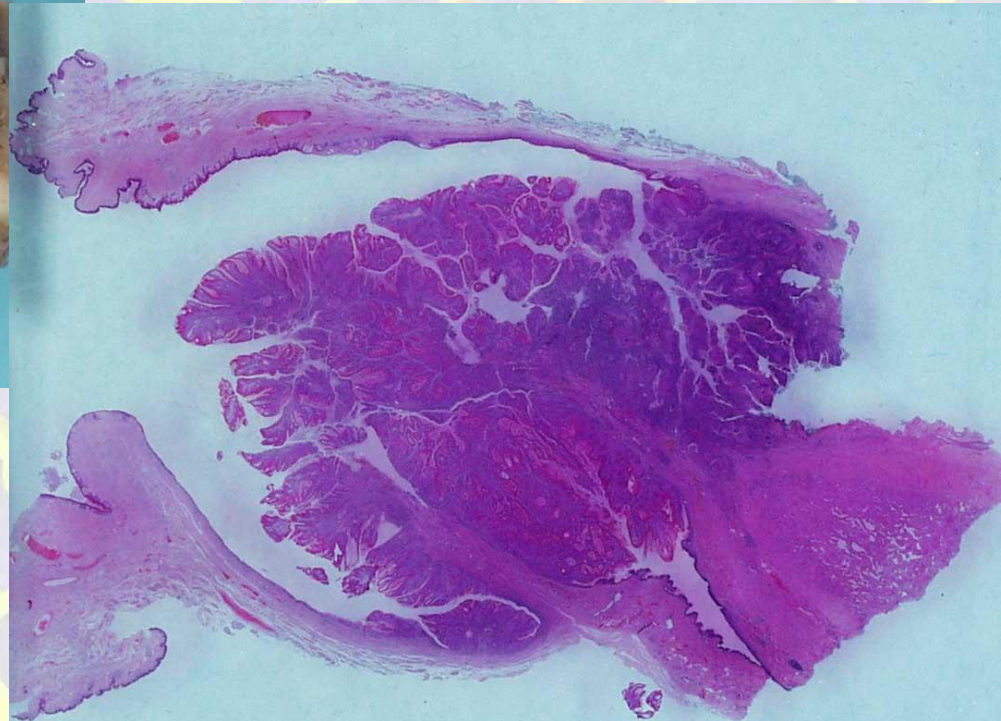
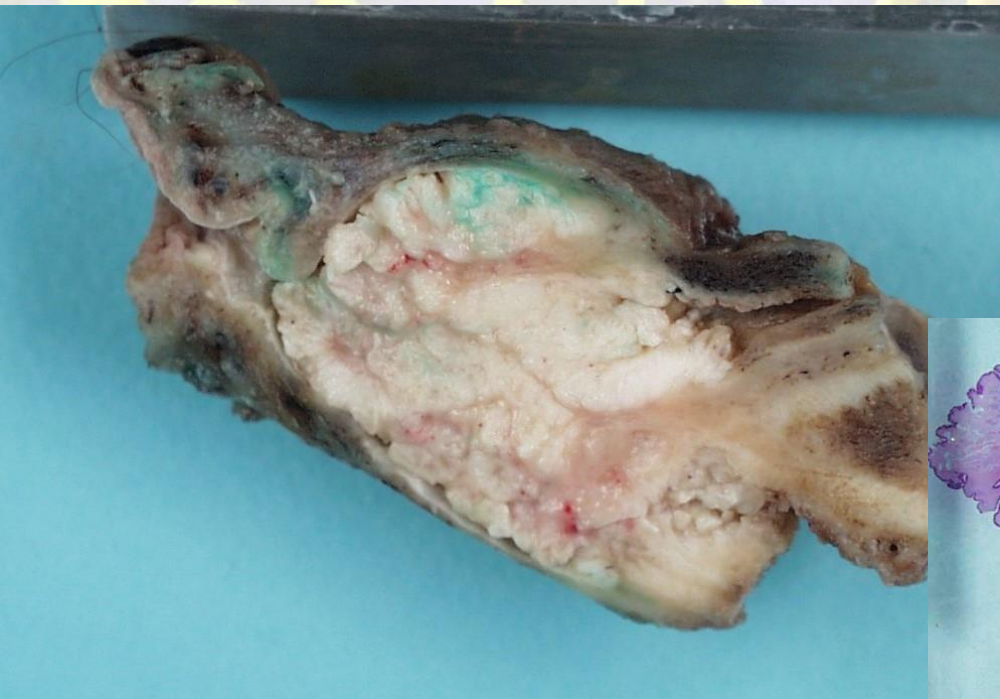
Warty Carcinoma

- Exophytic papillary/cauliflower like growth pattern
- Koilocytic cells present
- Not associated with LS but may be associated with warty undifferentiated PeIN and are P16 positive
- Usually well or moderately differentiated
- includes 'Bushke Lowenstein tumours' (giant condylomas) which are NOT benign
- Distinguished from warts by the presence of invasion and cytological atypia
- Good prognosis unless high grade or associated with Basaloid tumour

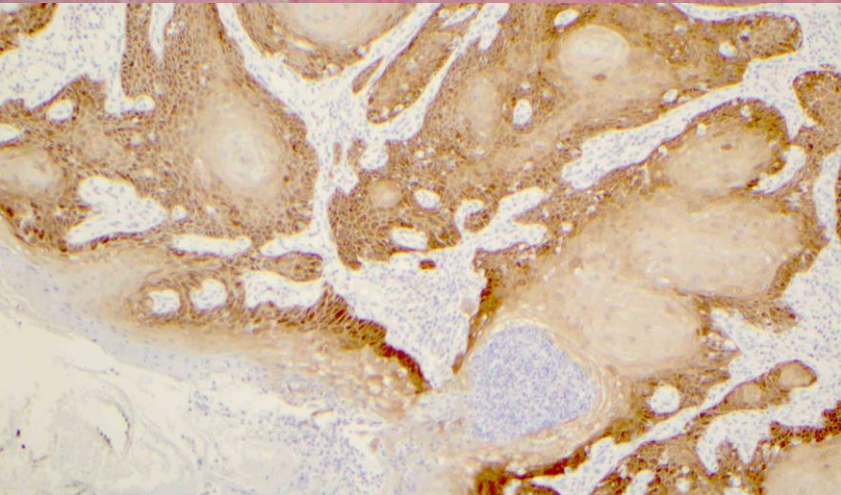
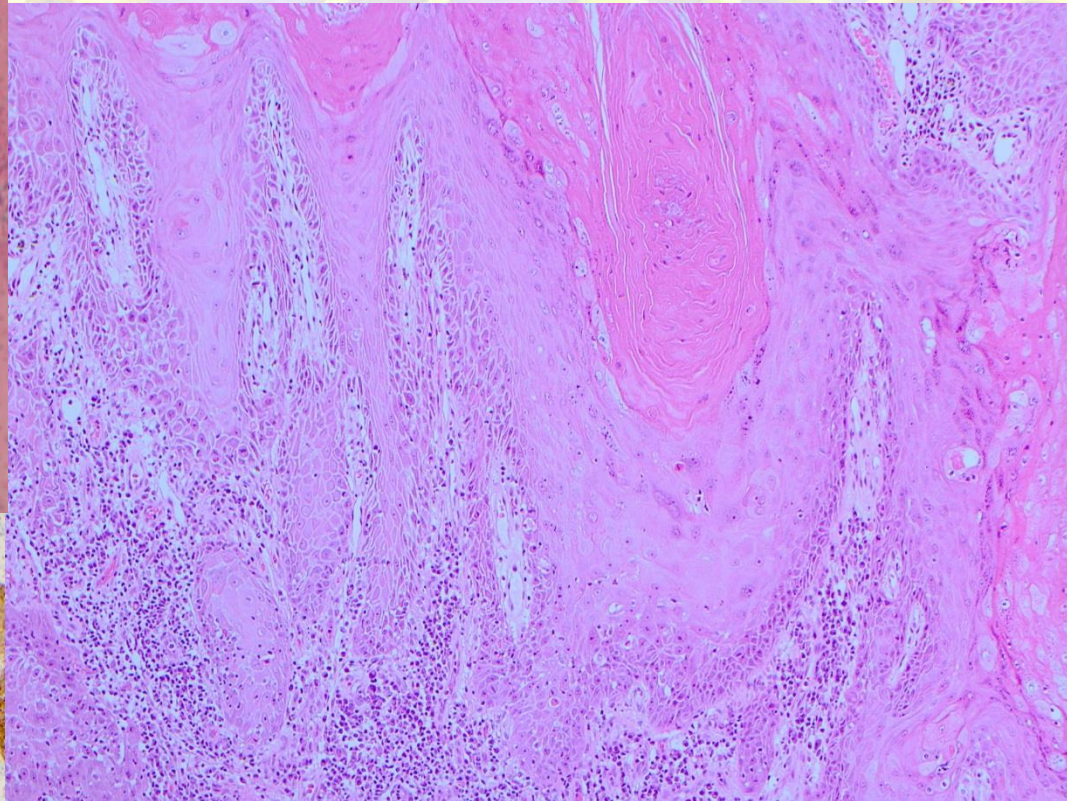
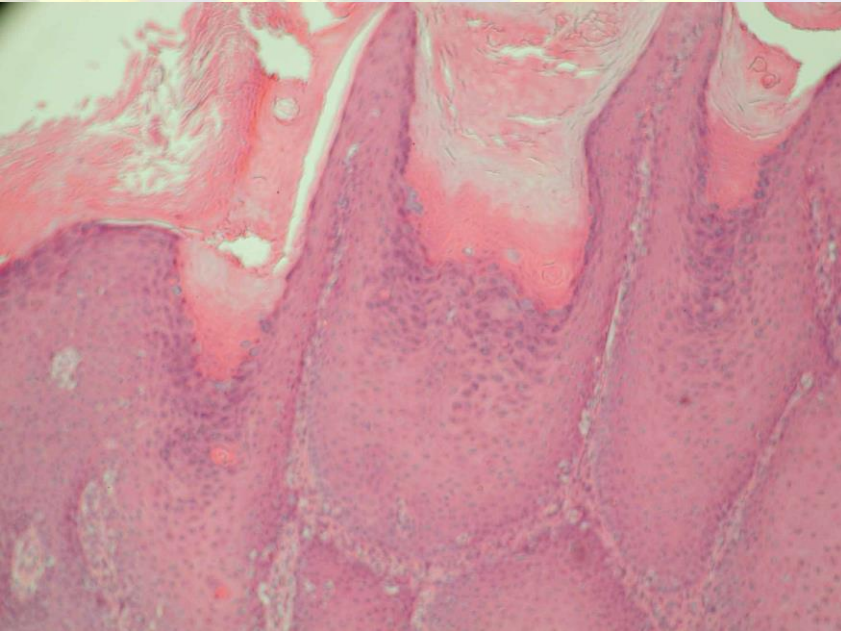
Warty Carcinomas of Glans and Foreskin



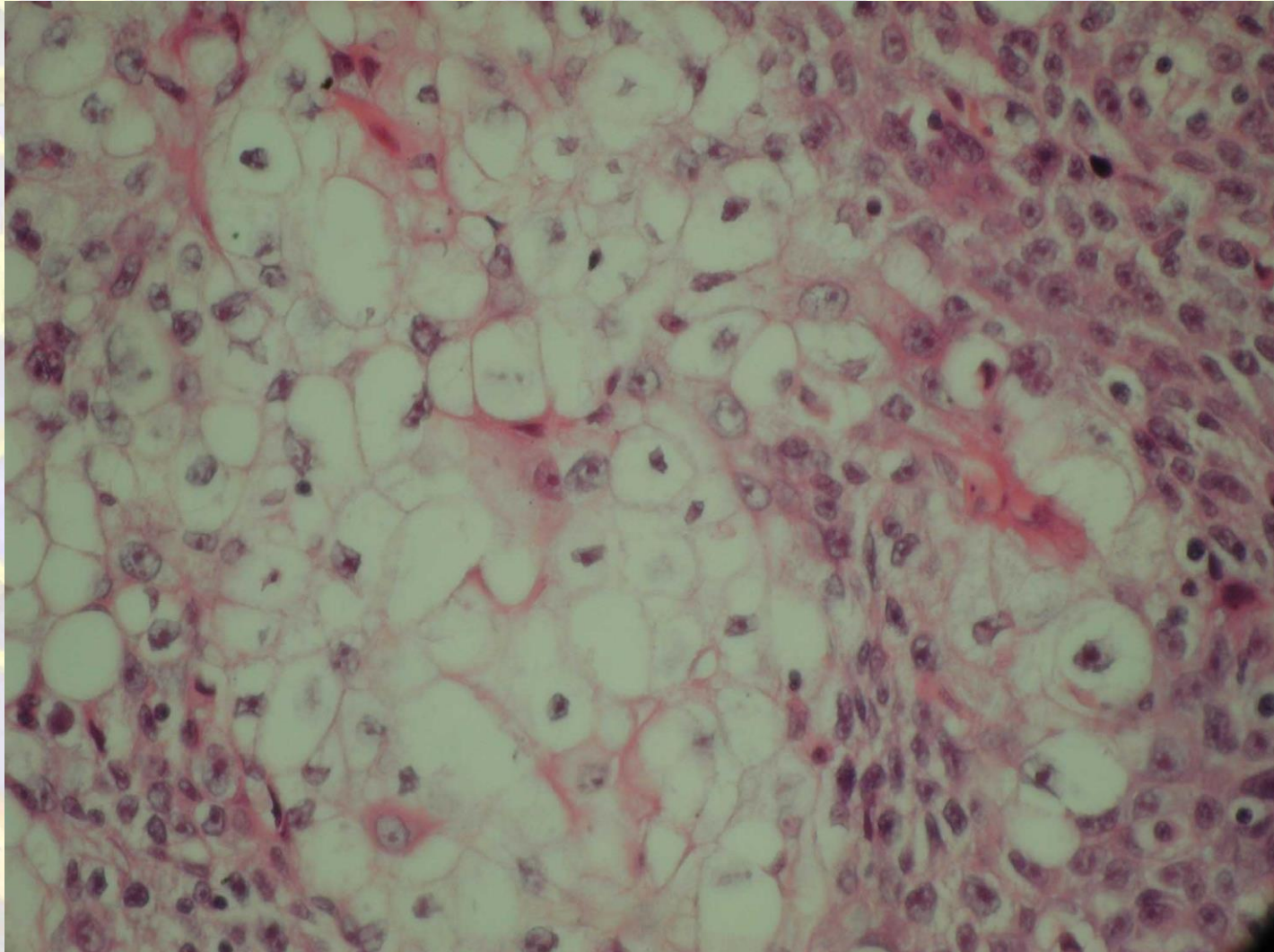
Warty carcinoma of Glans (‘Buschke Lowenstein tumour/Giant Condyloma’)



Warty Carcinoma – well differentiated on the surface – but invasive at the base. P16 positive



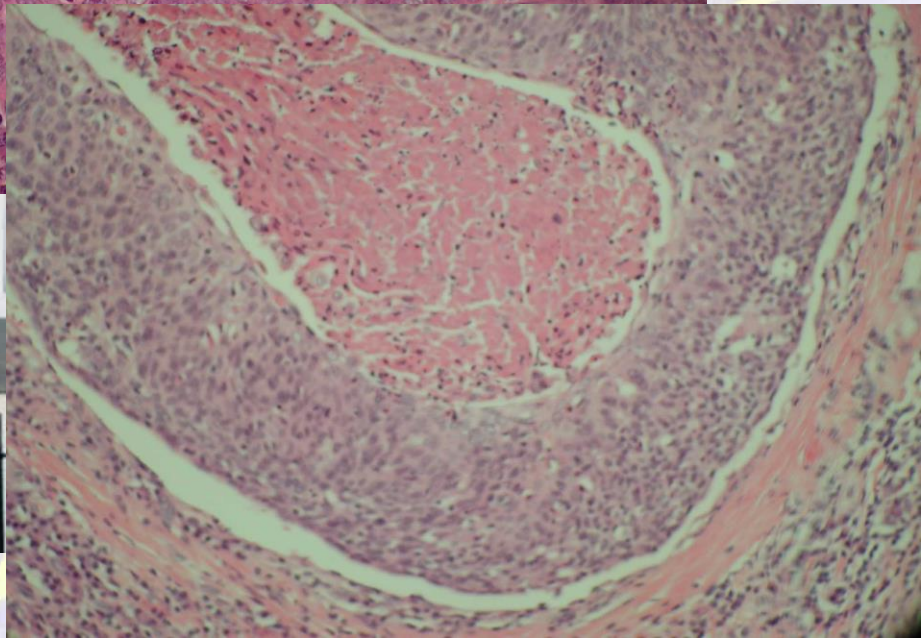
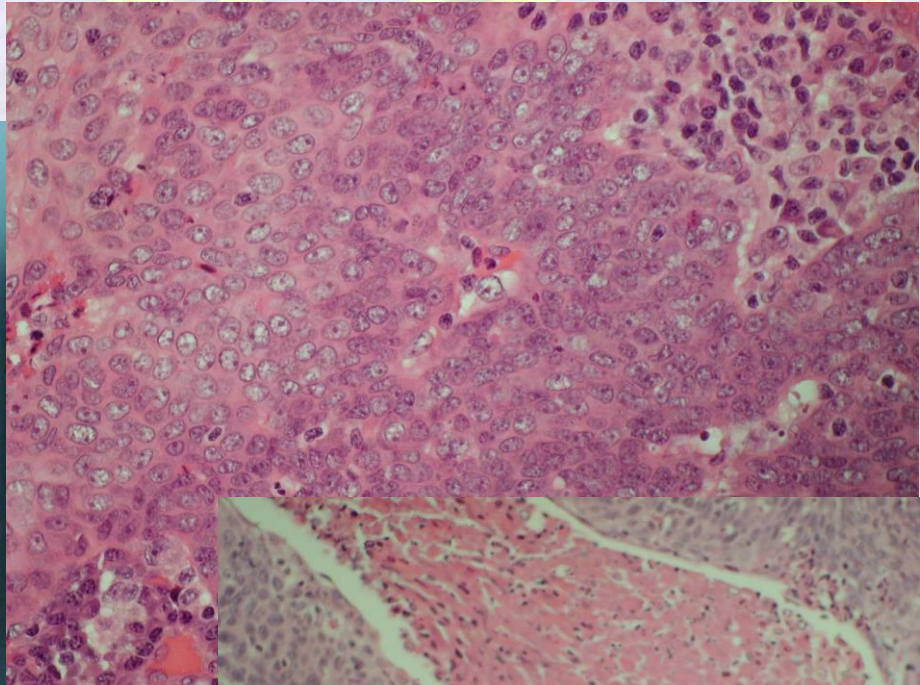
Warty carcinoma - clear cell variant



Basaloid SCC

- Aggressive high grade tumour
- 50% have nodal mets at the time of presentation
- Flat/ulcerated tumour with endophytic growth pattern
- Basaloid cells with abrupt comedo necrosis/keratinisation
- Associated with undifferentiated PeIN (Warty/Basaloid features)
- Associated with HPV and p16 positive
- Vascular invasion often present
- May metastasise to distant sites without inguinal lymph node involvement
- Often not recognised as a subtype by non specialist pathologists

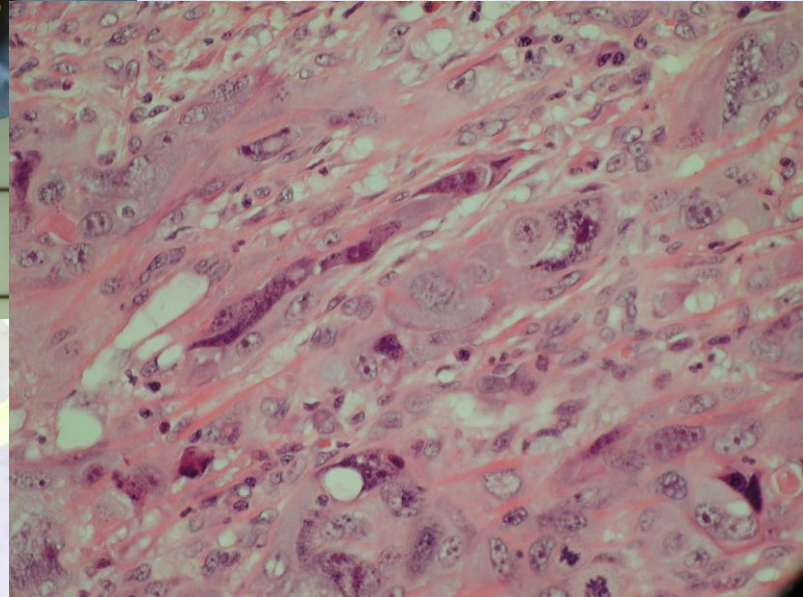
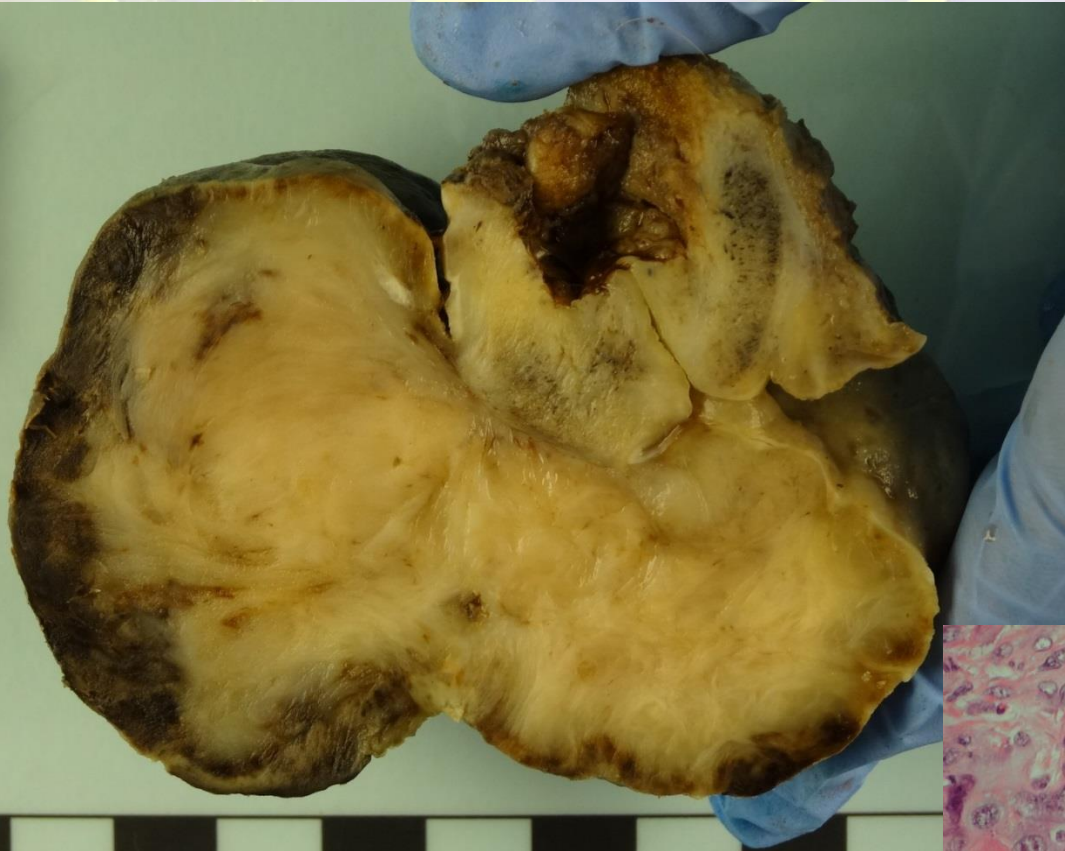
Basaloid carcinoma



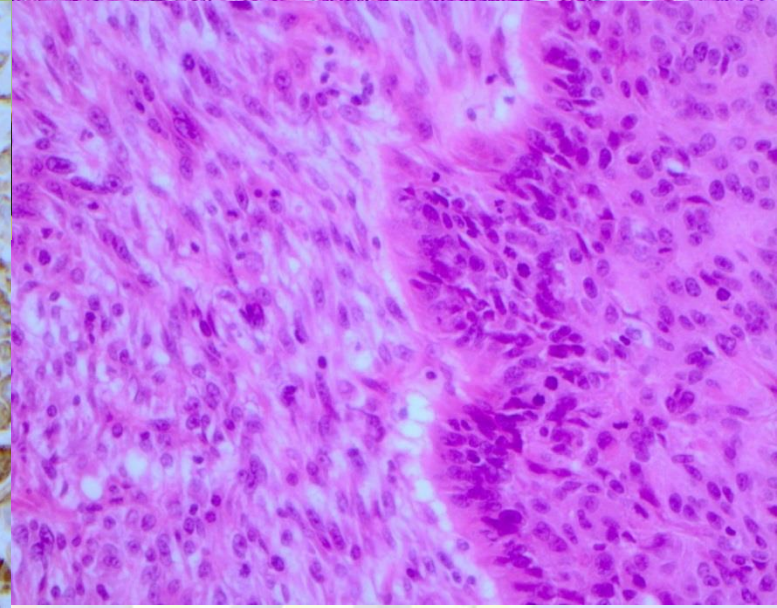
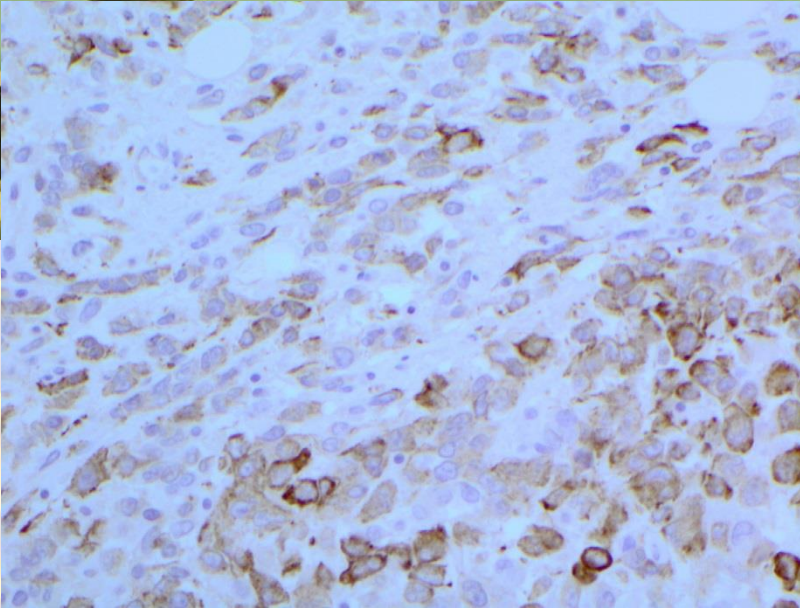
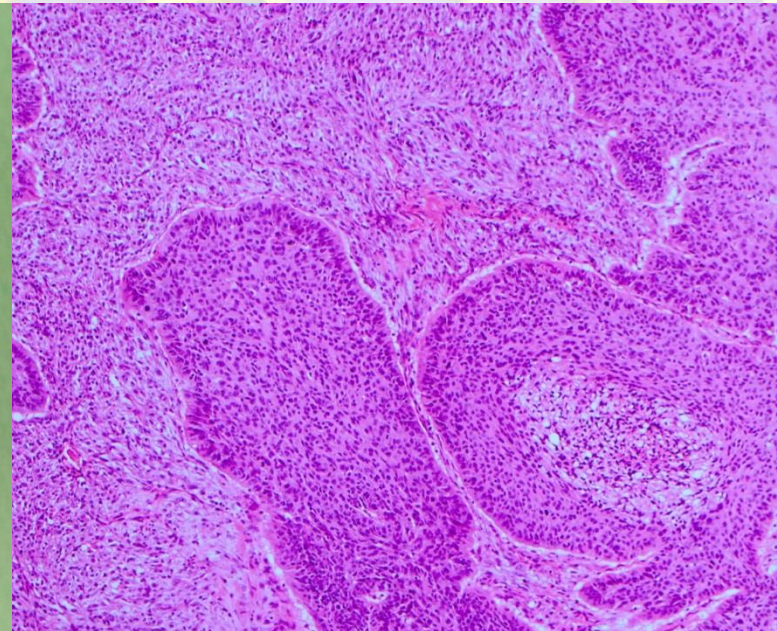
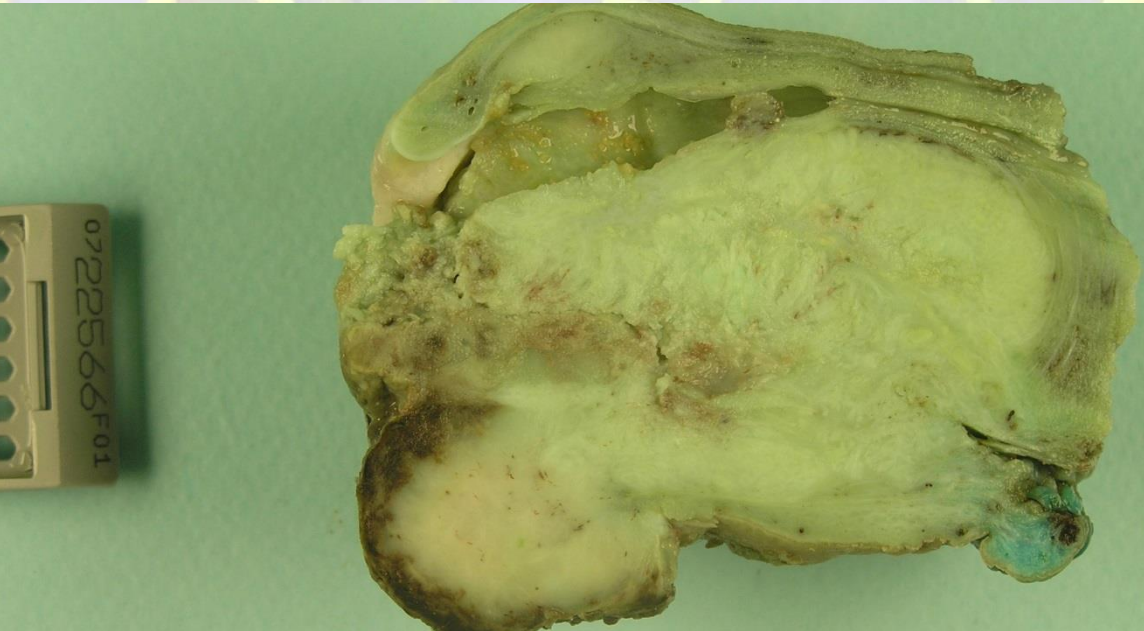
Sarcomatoid Squamous cell carcinoma

- High grade SCC with spindle cell differentiation in at least 30% of tumour
- Rare subtype, often mixed with other subtypes, often Verrucous carcinoma or usual SCC
- May contain pleomorphic/giant cells
- Rapid progression
- Very poor prognosis with distant mets at presentation
- Immunohistochemistry useful in distinguishing from Sarcoma (high MW keratins positive but may be very focal)

Sarcomatoid carcinoma



Sarcomatoid Carcinoma associated with Basaloid SCC. MNF116 and AE1/3 positive



Mixed tumours and typing/grading issues

- Up to 30% of tumours may show more than one pattern, all should be recorded in dataset.
- Focal high grade areas may co-exist within low grade tumours, making adequate sampling mandatory.
- Tumours are graded by worst area even if this is a minor component
- Grading is done on cytological features such as pleomorphism rather than by degree of keratinisation

Current TNM 7 (2010) Penile (Glans and Foreskin)

- TX Stage cannot be assessed
- Tis (in situ)
- Ta non invasive verrucous carcinoma
- T1a Subepithelial connective tissue without lymphovascular invasion and is not high grade
- T1b Subepithelial connective tissue with lymphovascular invasion and/or high grade
- T2 Corpus spongiosum /cavernosum
- T3 Urethra
- T4 Other adjacent structures and organs

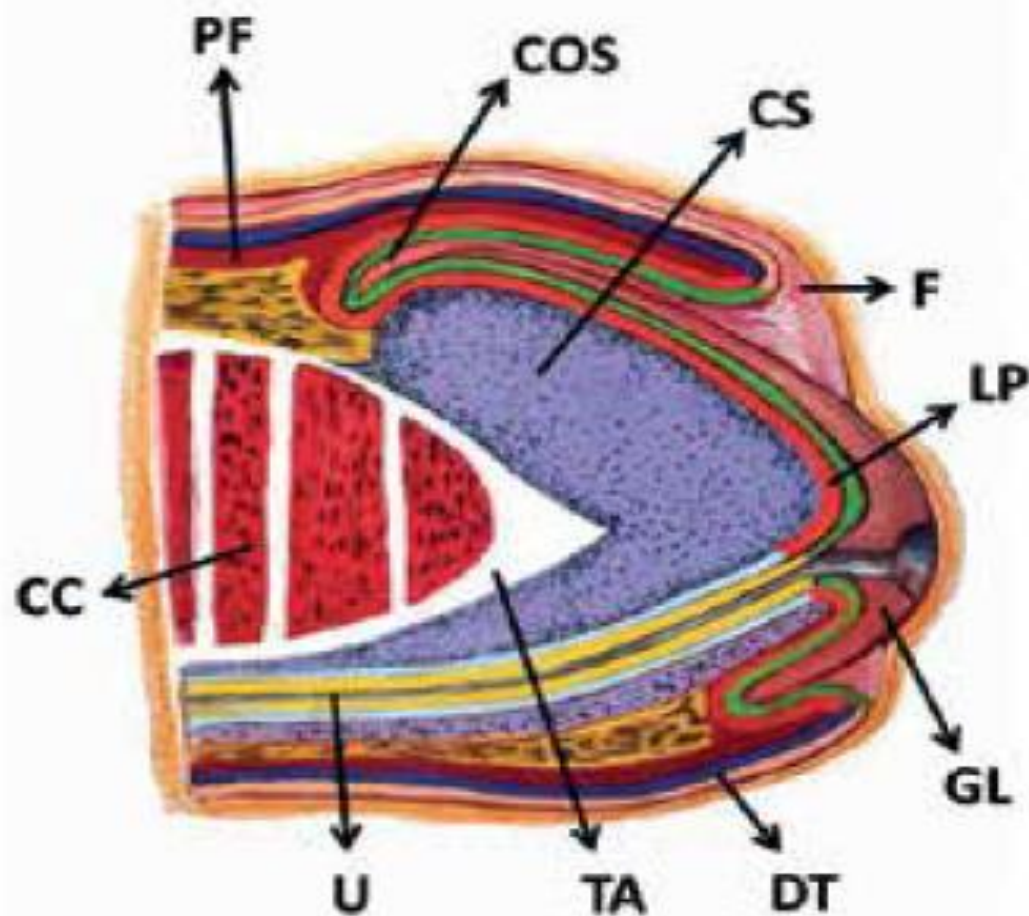


Fig. 5.01 Penile anatomy. The penile anatomical compartments are the glans (GL), foreskin (F), and coronal sulcus (COS). The anatomical levels are lamina propria (LP), corpus spongiosum (CS), dartos (DT), and corpus cavernosum (CC). The tunica albuginea (TA) is part of the corpus cavernosum. The penile fascia (PF) encases the shaft. The distal urethra (U) is ventral to the penis.

Issues with current Penile TNM7 Staging

- TX Stage cannot be assessed
 - Avoid use of this if possible, the terminology 'T1b at least' for example is preferable in incision biopsies or specimens with positive margins
- Tis (in situ) (PeIN)
- Ta ('non invasive verrucous carcinoma')
 - Not evidence based – not described in literature
 - Misleading as some pathologists may think this applies to all cases of verrucous carcinoma
 - The majority of verrucous carcinomas are invasive but assessment of invasion is difficult

Issues with Penile TNM7 staging

- T2 Corpus spongiosum/Cavernosum
- RCPATH guidelines recommend substaging of T2. (T2a Corpus spongiosum /T2b Corpora cavernosa)
- Good evidence that this is of prognostic significance
- When there is invasion of Corpora cavernosa this is usually associated with invasion of large vascular channels and greater metastatic potential
- **New TNM8 will probably stage tumours of Corpora cavernosa as T3**

Issues with Penile TNM staging

- T3 Urethral involvement
- Significance of urethral involvement alone not proven
- Involvement of Corpora cavernosa shown to be of more prognostic significance

T4 Other adjacent structures and organs

eg Scrotum, Perineum, Prostate, Testis etc

- Penile Skin? – shaft not considered T4
- Distal urethral tumours are not included and are currently staged using Urethral TNM
- How do we stage primary tumours of the shaft?
- New TNM8 (2016) has major pathological input (led by Mahul Amin)

The International Collaboration on Cancer Reporting (ICCR) guidelines on Penile and Distal Urethral tumours

- Australian led international dataset
- Steering group participants from USA, Canada, Australia, South America, UK and Europe
- Chaired by CC
- About to go out for consultation

What have we achieved so far

- New terminology and diagnostic criteria for PeIN
- Correct subtyping of tumours
- Demise of 'non invasive verrucous carcinoma and Buschke Lowenstein tumours' as diagnostic entities
- Staging to indicate involvement of Corpus cavernosum irrespective of urethral or spongiosum involvement
- Recognition of the relationships between distal urethral and penile tumours and their precursor lesions

Work in Progress

- Updates of datasets in 2016 to reflect new TNM8 for Penile tumours
- The new TNM for urethral tumours with distal tumours as a specific subset (?)
- Specialist review to become mandatory for supranetworks in UK

Developing specialist expertise 'The Hobnobs'

- Core members are lead specialist penile pathologists from UK Supranetworks
- Increasing number of international and research group members
- Educational and Research role for pathologists with a **major** interest in penile pathology
- Name of group devised to bypass Spam filters
- Meet annually usually at St George's in South London in January
- Slide Seminars and workshops
- Supranetwork review and second opinion service
- Subgroup of BAUP,
- Self funding (ie no funding at all)
- Not sponsored by McVities

