Update in Penile Pathology:- The New RCPPath Dataset and Diagnostic Pitfalls

Dr Cathy M Corbishley
Honorary Consultant Uropathologist
St George’s Hospital, London
Penile Carcinoma in the UK

- Penile cancer is rare with only 600 new cases in the UK per year – 10 per million population (1-3 per lab per year on average)
- The UK Urological Cancer Outcome Guidelines recommended management in a small number of supranetwork specialist centres serving a population of at least 4 million and managing at least 25 cases per year
- Since 2002 ten centres have become established in England and Wales
- Most centres are now seeing in excess of 50 new cases per year with St George’s seeing in excess of 125
Penile Carcinoma in the UK

• Most primary tumours are best treated surgically with radiotherapy and/or chemotherapy only used in the adjuvant and metastatic setting
• Centres require expertise in a wide range of techniques including reconstruction and plastic surgery
• First RCPath Penile dataset published in 2006 – (Pat Harnden, Alex Freeman and Cathy Corbishley)
• Supraregional centres on the same model have also been established in the Netherlands, Denmark and Sweden
The Penile and Distal Urethral dataset

Royal College of Pathologists Standards and datasets for reporting cancers

Dataset for penile and distal urethral cancer histopathology reports

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Authors: Dr Catherine Corbishley (lead author), St George’s Healthcare NHS Trust, London
Dr Jon Oxley, Southmead Hospital Bristol
Dr Jonathan H Shanks, The Christie NHS Foundation Trust, Manchester
Dr Brendan Tinwell, St George’s Healthcare NHS Trust, London
What’s new in the dataset

- Undifferentiated and Differentiated Penile Intraepithelial Neoplasia (PeIN)
- Subtyping including new tumour variants
- New surgical techniques including sentinel nodes and glans resurfacing
- The inclusion of a dataset for distal urethral tumours
- Use of modified TNM7 staging
- Diagrams to aid orientation, cut up, staging and margin assessment
Undifferentiated Penile Intraepithelial Neoplasia - PeIN

- Clinically usually flat erythematous lesions of glans and/or foreskin
- Undifferentiated PeIN (Penile intraepithelial neoplasia)
  Encompasses and replaces previous clinical terminology
  - Erythroplasia of Queyrat (mucosal)
  - Bowen’s disease (appendage bearing skin)
  - Squamous Carcinoma in situ
  - Severe Dysplasia
  - Bowenoid papulosis
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 sclerosus
- Associated with Usual type, Basaloid and Warty Carcinomas
Undifferentiated PeIN
Basaloid and Warty Basaloid
Bowenoid Papulosis

- Clinically defined condition – looks like multiple small benign warts
- **Multiple** small soft papular or macular lesions
- Usually on **shaft** in young men
- Less common on foreskin and glans
- Associated with HPV 16
- Histologically looks like warty/basaloid undifferentiated PeIN
- May regress spontaneously or with anti wart treatments
- May possibly progress to neoplasia in immunosuppressed individuals
- **Better to describe them 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
Multiple warty papules of the foreskin (and shaft) – could be Bowenoid papulosis
Precursor Lesions – Differentiated PeIN

- Clinically flat or slightly raised pale, white or erythematous lesions
- Similar to lesions seen in the Vulva
- Associated with Lichen sclerosus
- 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
Differentiated PeIN
Preneoplastic conditions of the Penis and PeIN terminology

- PeIN terminology should be used rather than clinical names.
- 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).
- 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 subtypes

- Tumour types seen are similar to tumours of anal and female genital region rather than those of the skin
- They also resemble the range of tumours seen in head and neck cancer
- Most tumours arise on the glans, with some arising on the foreskin and in the distal urethra
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 (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 non squamous tumours of the Penis

- Malignant melanoma (more usually Urethral primary)
- True Sarcomas and soft tissue tumours
- 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
- Lymphoreticular tumours
Tumour types associated with Lichen sclerosus and Differentiated PeIN

- Usual type SCCs
- Verrucous carcinoma and Carcinoma cuniculatum
- Pseudohyperplastic carcinoma
SCC – Usual type
Grades 2 and 3
Classic Verrucous carcinoma

- Always well differentiated and slow growing
- Associated with differentiated PeIN
- Associated with LS in 60% cases.
- P16 negative
- May be multifocal and recur locally
- Exophytic or burrowing invasion (broad based tumour islands without fibrovascular cores – ‘Elephants feet’)
- 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 sinuses
Verrucous Carcinoma associated with Lichen sclerosus
Verrucous Carcinoma of Foreskin with precursor lesions on glans
Verrucous Carcinoma of glans
Verrucous Carcinoma – an extreme longstanding case
Circumcised glansectomy showing Lichen sclerosus, differentiated PEIN and grade 1 pseudohyperplastic SCC)
Tumour types associated with Undifferentiated PeIN

- Usual type SCC
- Warty SCC
- Basaloid SCC
- Warty Basaloid SCC
Warty/Condylomatous 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. Usually P16 positive
Warty carcinoma with clear cell differentiation
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 16 and 18, but not Lichen sclerosus
- Tumours and PeIN are 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
- Rare subtype, often mixed with other subtypes, often Verrucous carcinoma or usual SCC
- May contain pleomorphic/giant cells
- Often deeply invasive
- Endophytic growth pattern
- 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
High grade Pseudoglandular (acantholytic) squamous carcinoma of foreskin
Mixed tumours and typing/grading issues

• Up to 30% of tumours may show more than one pattern, all should be recorded in dataset.
  – Verrucous and Usual
  – Warty Basaloid
  – Verrucous or Usual and Sarcomatoid
  – Warty and Clear cell

• Focal high grade areas may co-exist within low grade tumours, making adequate sampling mandatory.

• Tumours are graded by worst area

• The new WHO blue book is being published in 2016 with illustrations of all new entities
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
Distribution of Corpus spongiosum CS and Corpus cavernosum CC
Issues with current Penile TNM 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
  – Other tumours (eg Low grade warty and superficial papillary basaloid squamous cell carcinomas) are also rarely found to be non invasive
Issues with Penile TNM staging
Recommendation for substaging of pT2

• **T2a** Corpus spongiosum / **T2b** Corpora cavernosa

• Good evidence that this is of prognostic significance
• Several studies have now confirmed this.
• When there is invasion of Corpora cavernosa this is usually associated with invasion of large vascular channels
• **T2b** tumours more likely to metastasise
• **T2** substaging is included in the dataset as a core item
Issues with Penile TNM staging

- **T3 Urethral involvement**
  - subdivision needs evaluation, so not recommended as dataset core item
    - T3a Urethra within Glans
    - T3b Mid and Proximal Urethra, Prostate

- **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 staged using Urethral TNM

New TNM8 (2016) is being prepared and has major pathological input (led by Mahul Amin)
Surgical Treatment of the Primary

- Treatment plans depend on tumour type, grade and stage
- Low grade and superficial tumours may be treated radical circumcision, excision biopsy, glans resurfacing or glansectomy/limited partial penectomy (Penile preserving surgery)
- Partial penectomy and radical penectomy are less commonly performed now
"YOU RUDDY IDIOTS - I DIDN'T SAY I WISH I HAD A TWELVE INCH PIANIST!"

YE OLDE WISHING WELL
Radical Penectomy – a rare procedure, but sometimes still necessary
Radical penectomy, partial penectomy and glansectomy

Approximate surgical plane of incision for:
A - glansectomy (corporal heads may be included)
B - partial penectomy
C - radical penectomy
Circumcised and Uncircumcised
Partial penectomy/glansectomy specimen showing deep margins including periurethral corpus spongiosum, corporal heads and deep subcutaneous circumferential soft tissue.
Longitudinal section of partial penectomy showing distribution of corpus spongiosum within glans and periurethral tissues and resection margins.
Glansectomy with reconstruction
Glansectomy for foreskin tumour
Glansectomy with distal corpora for tumour of glans extending onto foreskin and involving distal urethra
Glans Resurfacing (for LS, PeIN and pT1a tumours)
Glans resurfacing specimen with direction of block taking indicated by vertical bars.

Peripheral cutaneous margin

Cut edges of glans segments (not true margins)

- Urethral meatus
- Coronal sulcus (ventral)

Surgical glans resurfacing technique

- Undifferentiated PeIN
- Not true margin
- Cutaneous margin
Glans resurfacing for superficial invasive tumour associated with LS
Distal partial penectomy for primary urethral tumour.

- Surgical procedure is the same but T staging differs.
- Basaloid tumours are commoner than usual type SCC at this site.
- Worse prognosis than glans and foreskin tumours
Penile TNM 7 staging - Nodes

- **pNX** Regional lymph nodes cannot be assessed.
- **pN0** No regional lymph node metastasis.
- **pN1** Metastasis in a single inguinal lymph node.
- **pN2** Metastases in multiple or bilateral inguinal lymph nodes.
- **pN3** Extranodal extension of lymph node metastasis (ECS) or involvement of pelvic lymph node(s) unilateral or bilateral.
- *(Nodal staging for distal urethral tumours does not include N3 category or mention of ECS)*
Surgical treatment of Lymph nodes

- Nodal dissections are reserved for Grade 2-3 tumours which are PT2 or greater, and G3pT1b tumours (EAU guidelines)
- Sentinel node techniques avoid the need for debilitating unnecessary node dissections in many cases (not yet available in every UK supranetwork – training and funding issues)
- Even small foci of ECS in inguinal nodal metastases convey a worse prognosis hence inclusion in T3 category in TNM7
Groin Dissection with nodes showing ECS
Sentinel Node Studies

• European Guidelines suggest that Grade 3 tumours of any stage and G2 pT2/3 tumours should have inguinal node dissections
• 60% of these will show no metastases and may well be overtreatment
• Inguinal node dissections are morbid procedures with long hospital stays and often complicated by lymphoedema
• Sentinel Node sampling at the same time as the definitive surgery prevents unnecessary operations and their complications
Sentinel node studies – injection site and high MW cytokeratins on a micrometastasis
Lymph node with ECS associated with perinodal fibrosis
Pathological assessment – Special Techniques

- Specimen photography – photography of glans and longitudinal cut section of specimen
- Careful differential marking of true resection margins (glans or cutaneous edges, true deep margins, corporal margins, circumferential margins, urethral margin)
- Large block sectioning and adequate sampling of tumour and margins
- Immunohistochemistry and cell proliferation markers are of limited usefulness in primary tumours except in sarcomatoid tumours and the odd melanoma.
- Immunohistochemistry with High MW keratins is routinely used for Sentinel node studies. Frozen sections are not recommended.
- P16 staining most useful for margin status of undifferentiated PeIN but not routinely indicated in tumours
- HPV testing not routinely indicated as has no implications for current treatment or prognosis
Dataset Items

- Tumour site of origin
- Tumour subtype
- Tumour dimensions
- Extent of invasion
- Modified TNM staging with subdivision of T2 to distinguish between Corpus spongiosum (2a) and cavernosum (2b) involvement
- Vascular invasion
- Perineural invasion
- Distance from nearest deep/lateral cutaneous and circumferential margins if 5mm or less
- Presence of associated PeIN
- Separate but related dataset for primary Urethral tumours
Diagnostic pitfalls

• Recognition of differentiated PeIN
• Recognition of Verrucous, low grade Warty carcinomas and Pseudohyperplastic carcinoma particularly in biopsies
• Difficulties with accurate staging, especially if large block sections are not used
• If in doubt get a specialist opinion (in the UK it will be reviewed by them anyway)
Should all Penile cancers be reviewed by a specialist Team?

- Referral of cases to a specialist multidisciplinary team is part of Improving Outcome Guidelines for Penile Cancer in the UK
- Does not specify Pathological Review (Yet!) but this is recommended in the dataset
- Every Urology team has to specify which supranetwork they refer penile cases to.
- Many non specialist pathologists do not subtype tumours, grade or stage correctly
- Verrucous, Pseudohyperplastic and Basaloid variants are often missed or underdiagnosed
- Differentiated PeIN is often unrecognised
- All Supranetwork lead Penile pathologists in the UK encourage central review and most offer a free expert referral service.
The UK Penile Pathology Group
(The Hobnobs)

- South London, South East and Central Southern England – St George’s (Brendan Tinwell) (Essex to Wessex)
- North London – UCH (Alex Freeman/Giorgia Trevisan)
- East Anglia – Norwich (Dani Peat)
- Midlands – Leicester (John Dormer) and Birmingham (Kin-Chung Wu)
- West of England – Bristol (Southmead) (Jon Oxley)
- Wales – Swansea (Ciaran O’Brien)
- North West England - Manchester (Christie) (Jonathan Shanks)
  - Wirral (Arrowe Park) (Ranjala Seneviratne)
- Yorkshire – Leeds (Selina Bhattaria)
- North East England – Gateshead (Matthew Theodosiou)
- Scotland – Glasgow (Jonathan Salmond)/Edinburgh (Paul Fineron)

International Members
- Eire – Cork (Nick Mayer)
- Research link – Dan Berney (Barts and the London)
- International Honorary Member – Dr Antonio Cubilla (Paraguay)
Thank You
Questions?