Protocol for the Examination of Specimens From Patients With Carcinoma of the Penis

Version: 4.2.0.0
Protocol Posting Date: September 2023
CAP Laboratory Accreditation Program Protocol Required Use Date: June 2024
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.
For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Penectomy	Includes specimens designated partial penectomy and total penectomy.
Circumcision	Required if margins can be assessed.
Tumor Type	**Description**
Carcinoma	Includes carcinomas arising from foreskin, glans, or penile shaft.

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy (incisional or excisional)
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Urothelial carcinoma (consider Urethra protocol)
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)
Sarcoma (consider the Soft Tissue protocol)

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
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Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- <u>Core data elements</u> are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is "not applicable" or "cannot be determined."
- <u>Conditional data elements</u> are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- <u>Optional data elements</u> are identified with "+" and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (i.e., secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
  - Anatomic site or specimen, laterality, and procedure
  - Pathologic Stage Classification (pTNM) elements
  - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

<u>Summary of Changes</u>

v 4.2.0.0

- WHO 5th Edition update to content and Explanatory Notes
- pTNM Classification update
- LVI question update from "Lymphovascular Invasion" to "Lymphatic and/or Vascular Invasion"

Reporting Template

Protocol Posting Date: September 2023
Select a single response unless otherwise indicated.

CASE SUMMARY: (PENIS)
Standard(s): AJCC-UICC 8
This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

SPECIMEN

Procedure (Notes A, B)
___ Incisional biopsy
___ Excisional biopsy
___ Glansectomy
___ Glans resurfacing
___ Partial penectomy
___ Total penectomy
___ Circumcision
___ Other (specify): _____
___ Not specified

Foreskin (presence and type) (Note C)
___ Not identified (circumcised)
___ Present (uncircumcised)
  +___ Short
  +___ Medium
  +___ Long
  +___ Phimotic
___ Cannot be determined: _____

TUMOR

+Tumor Focality (Note D)
___ Unifocal
___ Multifocal: _____

Tumor Site (Note E) (select all that apply)
___ Glans: _____
___ Foreskin mucosal surface: _____
___ Foreskin skin surface: _____
___ Coronal sulcus (balanopreputial sulcus): _____
___ Skin of the shaft: _____
___ Shaft: _____
___ Penile urethra: _____
___ Penis, NOS: _____

+Tumor Macroscopic Features (Note F) (select all that apply)
___ Flat
___ Ulcerated
___ Polypoid

___ Verruciform
___ Necrosis
___ Hemorrhage
___ Other (specify): _____

Tumor Size (Note G)
___ Greatest dimension in Centimeters (cm): _____ cm
   +Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _____

Histologic Type (Notes H, I)
___ HPV-independent squamous cell carcinoma
   ___ Squamous cell carcinoma, usual type (includes pseudohyperplastic and pseudoglandular)
   ___ Verrucous carcinoma
   ___ Papillary squamous cell carcinoma
   ___ Sarcomatoid squamous cell carcinoma
   ___ Mixed (specify): _____
   ___ Cannot be determined
___ HPV-associated squamous cell carcinoma
   ___ Basaloid squamous cell carcinoma
   ___ Warty carcinoma
   ___ Clear cell squamous cell carcinoma
   ___ Lymphoepithelial carcinoma
   ___ Medullary carcinoma
   ___ Mixed (specify): _____
   ___ Cannot be determined
___ Mixed HPV-independent HPV-associated squamous cell carcinoma (specify histologic types):
_____
Other Histologic Type
___ Squamous cell carcinoma, NOS (NOS and p16 stain is not available)
___ Adenosquamous carcinoma
___ Mucoepidermoid carcinoma
___ Paget disease
___ Adnexal carcinoma (specify type): _____
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined: _____
   +Histologic Type Comment: _____

Histologic Grade (Note J)
___ G1, well-differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ GX, cannot be assessed: _____
___ Other (specify): _____
___ Not applicable: _____
+Tumor Depth of Invasion / Thickness (Note K)
Specify in Millimeters (mm)
___ Depth of invasion (endophytic tumors): _____ mm
___ Thickness (exophytic and verruciform tumors): _____ mm

+Tumor Deep Borders (Notes L, M) (select all that apply)
___ Non-invasive
___ Invasive, broadly-based, pushing, non-destructive
___ Invasive, destructive but well-delineated front en bloc
___ Invasive, destructive, irregular, jagged
___ Other (specify): _____

Tumor Extent (Note N) (select all that apply)
___ Glans
  Select all that apply
  ___ Penile Intraepithelial Neoplasia (PeIN) or carcinoma in situ
  ___ Invades lamina propria
  ___ Invades corpus spongiosum
  ___ Invades tunica albuginea
  ___ Invades corpus cavernosum
  ___ Invades penile (Buck's) fascia
___ Foreskin
  Select all that apply
  ___ Penile Intraepithelial Neoplasia (PeIN) or carcinoma in situ
  ___ Invades lamina propria
  ___ Invades dartos
  ___ Invades dermis
  ___ Invades epidermis
___ Shaft or body
  Select all that apply
  ___ Invades dermis
  ___ Invades dartos
  ___ Invades penile (Buck's) fascia
  ___ Invades tunica albuginea
  ___ Invades corpus cavernosum
___ Extension beyond penis
  Select all that apply
  ___ Invades regional skin (pubis, inguinal)
  ___ Invades adjacent structure(s) (i.e., scrotum, prostate, pubic bone) (specify): _____
  ___ Invades other structure(s) (specify): _____
  ___ Cannot be determined (explain): _____
___ No evidence of primary tumor

Lymphatic and / or Vascular Invasion (Note O)
___ Not identified
___ Present
___ Cannot be determined: _____

Perineural Invasion (Note P)
___ Not identified
___ Present
___ Cannot be determined: _____

+Tumor Comment: _____

MARGINS (Note Q)

Margin Status for Invasive Carcinoma
___ All margins negative for invasive carcinoma
  +Closest Margin(s) to Invasive Carcinoma (select all that apply)
  ___ Urethral: _____
  ___ Periurethral tissues (subepithelial connective tissue [lamina propria], corpus spongiosum, Buck's
  fascia): _____
  ___ Corpus cavernosum: _____
  ___ Buck's fascia at penile shaft: _____
  ___ Skin: _____
  # For circumcision specimens only
  ___ Coronal sulcus mucosal#: _____
  ___ Cutaneous#: _____
  ___ Other (specify): _____
  ___ Cannot be determined (explain): _____
  +Distance from Invasive Carcinoma to Closest Margin
  Specify in Millimeters (mm)
  ___ Exact distance: _____ mm
  ___ Greater than: _____ mm
  ___ At least (specify): _____ mm
  ___ Less than: _____ mm
  ___ Less than 1 mm
  ___ Other (specify): _____
  ___ Cannot be determined: _____
___ Invasive carcinoma present at margin
  Margin(s) Involved by Invasive Carcinoma (select all that apply)
  ___ Urethral: _____
  ___ Periurethral tissues (subepithelial connective tissue [lamina propria], corpus spongiosum, Buck's
    fascia): _____
  ___ Corpus cavernosum: _____
  ___ Buck's fascia at penile shaft: _____
  ___ Skin: _____
  # For circumcision specimens only
  ___ Coronal sulcus mucosal#: _____
  ___ Cutaneous#: _____
  ___ Other (specify): _____
  ___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

Margin Status for Noninvasive Carcinoma / Carcinoma in Situ
___ All margins negative for non-invasive carcinoma / carcinoma in situ
___ Noninvasive carcinoma / carcinoma in situ present at margin
  Margin(s) Involved by Noninvasive Carcinoma / Carcinoma in Situ
  ___ Specify involved margin(s): _____
  ___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES (Note R)

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
  ___ All regional lymph nodes negative for tumor
  ___ Tumor present in regional lymph node(s)
   Number of Lymph Nodes with Tumor
   ___ Exact number (specify): _____
   ___ At least (specify): _____
   ___ Other (specify): _____
   ___ Cannot be determined (explain): _____
   Nodal Site(s) with Tumor (select all that apply)
   ___ Sentinel: _____
   ___ Inguinal: _____
    Number of Inguinal Lymph Nodes with Tumor
    ___ Exact number (specify): _____
    ___ At least (specify): _____
    ___ Other (specify): _____
    ___ Cannot be determined (explain): _____
    Laterality of Inguinal Lymph Node(s) with Tumor
    ___ Unilateral
    ___ Bilateral
    ___ Cannot be determined (explain): _____
   ___ Pelvic: _____
   ___ Other (specify): _____
   ___ Cannot be determined
   +Size of Largest Nodal Metastatic Deposit
   Specify in Centimeters (cm)
   ___ Exact size: _____ cm
   ___ At least (specify): _____ cm
   ___ Greater than: _____ cm
   ___ Less than: _____ cm
   ___ Other (specify): _____
   ___ Cannot be determined (explain): _____
   +Nodal Site with Largest Metastatic Deposit (specify site): _____

   +Size of Largest Lymph Node with Tumor
   Specify in Centimeters (cm)
   ___ Exact size: _____ cm
   ___ At least (specify): _____ cm
   ___ Greater than: _____ cm
   ___ Less than: _____ cm
   ___ Other (specify): _____
   ___ Cannot be determined
   +Largest Lymph Node with Tumor (specify site): _____
   Extranodal Extension
   ___ Not identified

___ Present
    ___ Cannot be determined: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS (Note S)

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Site(s) outside the true pelvis: _____
___ Lung: _____
___ Heart: _____
___ Liver: _____
___ Cutaneous nodules distant from the primary site: _____
___ Bone: _____
___ Other (specify): _____
___ Cannot be determined: _____

pTNM CLASSIFICATION (AJCC 8th Edition) (Note T)
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Modified Classification (required only if applicable) (select all that apply)
___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category
___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma *in situ* (Penile intraepithelial neoplasia [PeIN])
___ pTa: Noninvasive localized squamous cell carcinoma
pT1: (Glans) Tumor invades lamina propria; (Foreskin) Tumor invades dermis, lamina propria, or dartos fascia; (Shaft) Tumor invades connective tissue between epidermis and corpora regardless of location; All sites with or without lymphovascular invasion or perineural invasion and is or is not high grade
___ pT1a: Tumor is without lymphovascular invasion or perineural invasion and is not high grade (i.e., grade 3 or sarcomatoid)
___ pT1b: Tumor exhibits lymphovascular invasion and / or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid)
___ pT1 (subcategory cannot be determined)
___ pT2: Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion
___ pT3: Tumor invades into corpora cavernosum (including tunica albuginea) with or without urethral

invasion
___ pT4: Tumor invades into adjacent structures (i.e., scrotum, prostate, pubic bone)

T Suffix (required only if applicable)
___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No lymph node metastasis
___ pN1: less than or equal to 2 unilateral inguinal metastases, no extranodal extension
___ pN2: greater than or equal to 3 unilateral inguinal metastases or bilateral metastases, no ENE
___ pN3: Extranodal extension of lymph node metastases or pelvic lymph node metastases

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
 # Including lymph node metastasis outside the true pelvis, lung, liver, cutaneous nodules distant from the primary site, and bone.
___ pM1: Distant metastasis present#

ADDITIONAL FINDINGS (Note U)

+Additional Findings (select all that apply)
___ None identified
___ HPV-associated penile intraepithelial neoplasia (PeIN)
   Select all that apply
   +___ Basaloid (undifferentiated)
   +___ Warty (condylomatous, bowenoid)
   +___ Pagetoid
   +___ Clear cell
   +___ Mixed (specify): _____
___ HPV-independent differentiated penile intraepithelial neoplasia (PeIN)
___ Lichen sclerosus
___ Squamous hyperplasia
___ Condyloma acuminatum
___ Mixed HPV associated-HPV independent
___ Other (specify): _____

SPECIAL STUDIES (Note V)

+p16 Immunohistochemistry
___ Positive
___ Negative

+HPV-ISH
___ Positive, high risk, NOS
___ Positive, low risk, NOS
___ Negative

+Other Ancillary Studies
___ Specify: _____
___ Not performed

COMMENTS

Comment(s): _____

Explanatory Notes

A. Procedure
Surgeons often perform small or superficial penile biopsies that are difficult to classify as benign or malignant, and if malignant, cannot always be accurately subclassified. In a study, biopsy failed to identify the correct histologic grade in 30% of the cases and a higher grade was usually identified in subsequent penectomy specimens. Because biopsies were superficial, the deepest point of invasion could not be determined in 91% of the cases. Vascular invasion was identified in biopsies in only 1 of 8 patients. Biopsies were useful only for cancer diagnosis in 95% of the cases. Cancer diagnosis is difficult in grade 1 verruciform tumors. Important pathologic parameters related to prognosis are missed on biopsy materials, and they are more accurately evaluated in penectomy specimens. Clinical and pathologic staging of penile cancer cannot depend on biopsy information alone.[1] Surgical penile preserving therapy is resulting in not infrequent small specimens. The aim is to conserve as much penile tissue for functional integrity without compromising oncological control. Low-grade superficial tumors invading up to lamina propria can be treated by local excision. Glans resurfacing can be used for lichen sclerosus and especially for the excision of glans Penile Intraepithelial Neoplasia. Glansectomy (partial or total) is used for low-grade cancers exclusive of the glans and invading up to corpus spongiosum.[2,3,4,5]

References
1. Velazquez EF, Barreto JE, Rodriguez I, et al. Limitations in the interpretation of biopsies in patients with penile squamous cell carcinoma. *Int J Surg Pathol. 2004*;12:139-146.
2. Tang DH, Yan S, Ottenhof SR, et al. Glansectomy as Primary Management of Penile Squamous Cell Carcinoma: An International Study Collaboration. *Urology.* 2017;109:140-144.
3. Fang A, Ferguson J. Penile Sparing Techniques For Penile Cancer. *Postgrad Med.* 2020;132;42-51.
4. Pang KH, Alnajjar HM, Muneer A. Advances in penile-sparing surgical approaches. *Asian J Urol.* 2022;9:359-373.
5. Peyraud F, Allenet C, Gross-Goupil M, et al. Current management and future perspectives of penile cancer: An updated review. *Cancer Treat Rev.* 2020;90,102087.

B. Handling of the Specimen
Circumcision Specimen (Figure 1)
Take measurements, describe specimen, and identify and describe tumor. Identify and ink the mucosal and cutaneous margins with different colors. Most SCCs arise from the mucosal surface of the foreskin, therefore the coronal sulcus (mucosal) margin is especially important. Lightly stretch and pin the specimen to cardboard. Fix for several hours in formalin. Cut vertically the whole specimen labeling from 1 to 12, clockwise.
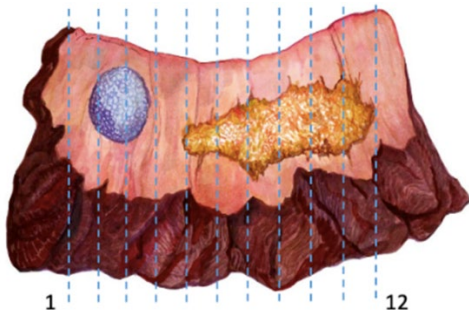

Figure 1. Foreskin vertical sectioning method in a biphasic pseudohyperlastic (right) and verrucous (left) carcinomas.

Resurfacing and Glansectomies (Figures 2 and 3)

The glans surface is marked by the surgeon into four quadrants radiating out from the meatus to the coronal sulcus. The glans mucosa is dissected out between the subepithelial tissues and corpus spongiosum although often small areas of corporal tissue are found attached to the specimen which measure 0.5-2mm in thickness (Corbishley Seminars). In glansectomies there are no special anatomical indications and sections should be made perpendicular to the tumor in sequential slices inking the deep resection margin which is usually at the level of corpus spongiosum, but a portion of the tunica albuginea may be present.
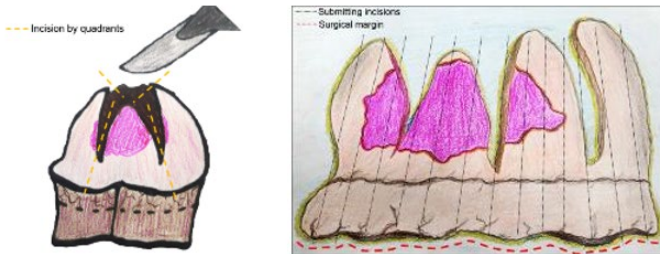
Figure 2. Resurfacing specimen (lesion indicated in purple). Glans surface incisions in quadrants before resection (A). After resection, margins are indicated in red (B). Submit tissue in sequence as indicated by the vertical lines (Courtesy of Dr. C. Corbishley).
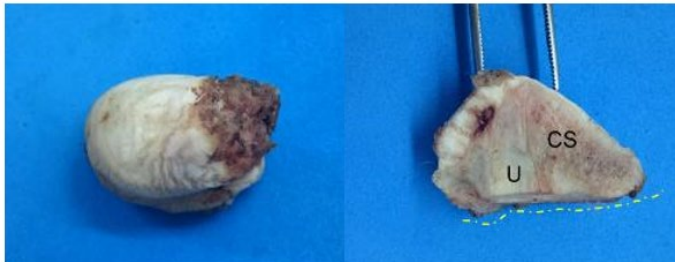
Figure 3. Glansectomy specimen. Exophytic tumor on glans surface (A). After sectioning, tumor is white with sharply delineated front (B). Histology showed a verrucous carcinoma. Corpus spongiosum (CS) and urethra (U) are not involved. Surgical margin is denoted in broken lines.

Penectomy Specimen (Figures 4 and 5)

Take measurements, describe specimen, and identify and describe tumor. Most SCCs of the penis arise from the epithelium of the distal portion of the organ (glans, coronal sulcus, and mucosal surface of the prepuce; the tumor may involve one or more of these anatomical compartments) If present, classify the foreskin as short, medium, long, and/or phimotic. Cut the proximal margin of resection en face making sure to include the entire circumference of the urethra (Figure 5). If the urethra has been retracted, it is important to identify its resection margin and submit it entirely. The resection margin can be divided into three important areas that need to be analyzed: the skin of the shaft with underlying dartos and penile fascia; corpora cavernosa with albuginea; and urethra with periurethral cylinder that includes subepithelial connective tissue (lamina propria), corpus spongiosum, albuginea, and penile fascia (Figure 5). The urethra and periurethral cylinder can be placed in one cassette. The skin of the shaft with dartos and fascia can be included together with the corpora cavernosa. Because this is a large specimen, it may need to be included in several cassettes to include the entire resection margin. Fix the rest of the specimen overnight. Then, in the fixed state and if the tumor is large and involves most of the glans, cut longitudinally and centrally by using the meatus and the proximal urethra as reference points. Do not probe the urethra. Separate the specimen into halves, left and right. Then cut two to six serial sections of each half. If the tumor is small and asymmetrically located in the dorsal or ventral area, the central portion

of the tumor may be used as the axis of sectioning. If the tumor is large involving multiple sites (glans, sulcus, and foreskin), it is important not to remove the foreskin leaving the entire specimen intact for sectioning.

In cases of small carcinomas exclusively located in the glans with no foreskin involvement, one may choose to remove the foreskin leaving a 3-mm redundant edge around the sulcus. Proceed cutting the foreskin as indicated for circumcision specimens. If the primary tumor is located in the glans, one should still submit the foreskin serially and in an orderly fashion labeled from 1 to 12 clockwise. The rest of the penectomy specimen should be handled as described above.
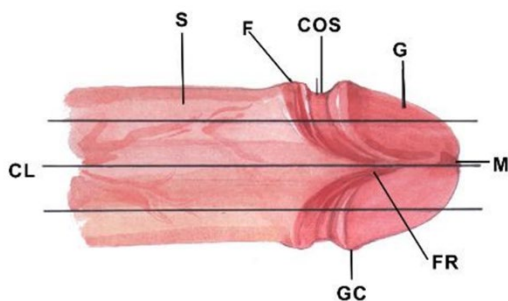
Figure 4. Partial penectomy specimen. Vertical lines indicate anatomical sites. Horizontal lines indicate sectioning method, central and sagittal. S, Shaft; F, foreskin; COS, coronal sulcus; G, glans; M, meatus; FR, frenulum; GC, glans corona; CL, center line.
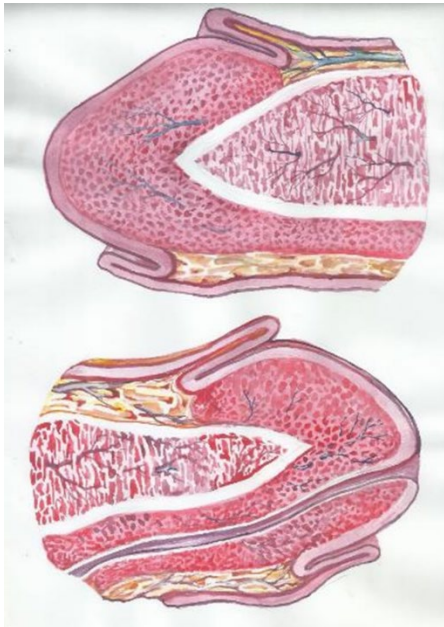
Figure 5. Cut surface of partial penectomy specimen. Above there is the sagittal cut. All anatomical layers from glans, coronal sulcus, and foreskin are grossly evident. Below is the central cut with urethra separating superior from inferior glans.

C. Types of Foreskin

There are three foreskin types (Figure 6): in the short foreskin, the preputial orifice is located behind the glans corona; in the medium foreskin, the orifice is between the corona and the meatal orifice; in the long foreskin, the entire glans is covered and the meatus is not identified without retracting the foreskin. Phimotic foreskins are unretractable and long.[1] Phimosis is present in up to one-half of patients with penile carcinoma[1], and its presence is considered a risk factor for the development of this tumor.[2,3,4]
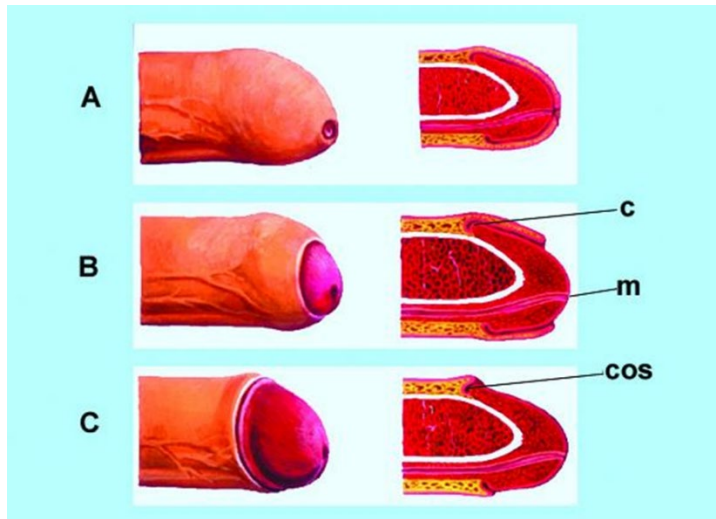
Figure 6. Types of foreskin, long (A), medium (B) and short (C). C, corona; M, meatus; COS, coronal sulcus.

References

1. Velazquez EF, Bock A, Soskin A, Codas R, Arbo M, Cubilla AL. Preputial variability and preferential association of long phimotic foreskins with penile cancer: an anatomic comparative study of types of foreskin in a general population and cancer patients. *Am J Surg Pathol*. 2003;27(7):994-998.
2. Daling J, Madeleine MM, Johnson LG, et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. *Int J Cancer.* 2005;116(4):606-616.
3. Tsen HF, Morgenstern H, Mack T, Peters RK. Risk factors for penile cancer: results of a population-based case-control study in Los Angeles County (United States). *Cancer Causes Control.* 2002;12(3):267-277.
4. Madsen BS, van den Brule AJ, Jensen HL, Wholfahrt J, Frisch M. Risk factors for squamous cell carcinoma of the penis: population-based case-control study in Denmark. *Cancer Epidemiol Biomarkers Prev.* 2008;17(10):2683-2691.

D. Tumor Focality

Focality refers to one (unifocal) or more (multifocal) independent primary tumors in the same specimen or anatomical site. Multifocal tumors are separated by non-neoplastic tissue. A whole organ section with tridimensional reconstruction is required to qualify a tumor as multifocal. Multicentricity is a clinical or gross concept and it refers to the non-tridimensional observation of more than one tumor in the same specimen detected in routine sections. Most invasive penile carcinomas are unifocal, but about 8-10% of the cases present as multifocal lesions.[1] Primary preputial carcinomas tend to be multifocal, especially those associated with extensive lichen sclerosus. A prototype is the Pseudo-hyperplastic variant of squamous cell carcinoma (Figure 7).[2] Compared with invasive carcinomas, PeIN lesions are more

frequently multifocal in various sites (glans, sulcus, foreskin, and/or skin of the shaft), especially those associated with HPV.[3,4]
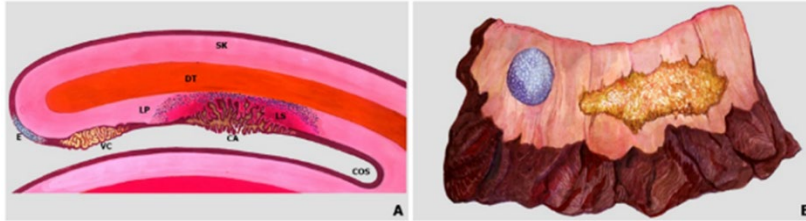

Figure 7. Multicentric tumors: pseudohyperplastic carcinoma of the foreskin (A) and verrucous carcinoma (B) associated with lichen sclerosus. SK (skin), DT (dartos), LP (lamina propria), E (epithelium with squamous hyperplasia), VC (verrucous carcinoma), CA (pseudohyperplastic carcinoma, COS (coronal sulcus).

References
1. Cubilla AL, Barreto J, Caballero C, et al. Pathologic features of epidermoid carcinoma of the penis. A prospective study of 66 cases. *Am J Surg Pathol.* 1993;17:753-763.
2. Cubilla AL, Velazquez EF, Young RH. Pseudohyperplastic squamous cell carcinoma of the penis associated with lichen sclerosus. An extremely well-differentiated, nonverruciform neoplasm that preferentially affects the foreskin and is frequently misdiagnosed: a report of 10 cases of a distinctive clinicopathologic entity. *Am J Surg Pathol.* 2004;28:895-900.
3. Oertell J, Caballero C, Iglesias M, et al. Differentiated precursor lesions and low-grade variants of squamous cell carcinomas are frequent findings in foreskins of patients from a region of high penile cancer incidence. *Histopathology.* 2011;58:925-933.
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E. Tumor Site
Tumor sites are the glans, coronal sulcus, foreskin, the skin of the shaft, and penile (distal) urethra (Figure 8). Unlike urothelial tumors arising in the proximal urethra, more than half of tumors arising in the penile urethra are non-urothelial and morphologically indistinguisible from tumors originating in the glans.[1,2] The information on tumor location is scant, variable, or not very reliable. The reasons are the lack of knowledge of penile anatomy, the lack of interest of clinicians and pathologists to precisely define the site of the tumor, the confusion of location with sites of origin, and, especially, in regions endemic for penile cancer, the large size of tumors affecting more than one site and effacing the normal boundaries of the anatomical compartments. In one prospective study, 56% of all cancer cases involved multiple compartments.[3] Excluding these large neoplasms, where sites of involvement are not clear, the majority of penile squamous cell carcinomas originate in the glans (80%), foreskin (15%), or coronal sulcus (Figures 9 and 10).[4,5,6]Tumors arising in the skin of the shaft[7] or outer surface of the foreskin are most unusual). We have not seen tumors arising in the foreskin outer surface skin. Site of origin is not synonymous with tumors involving anatomical sites. There are tumors with superficially spreading or multicentric patterns that may affect or originate in more than one compartment.[6] To evaluate prognosis by anatomical site, only tumors compromising one epithelial compartment should be considered.

The main reason for establishing site of tumor as a required data for the pathology report is that carcinomas exclusive of the foreskin are associated with a better prognosis than those limited to the glans. Circumcision is the most common treatment modality for carcinomas of foreskin, and recurrences were reported to be less frequent in foreskin carcinomas than in those of glans.[8] Glans carcinomas are

comparatively of higher grade, associated with HPV and with infiltration of deeper anatomical layers. Carcinomas of the foreskin are less likely to be associated with HPV than glans carcinomas, are more likely to be associated with lichen sclerosus, and show a lower frequency of regional metastasis.[9,10]
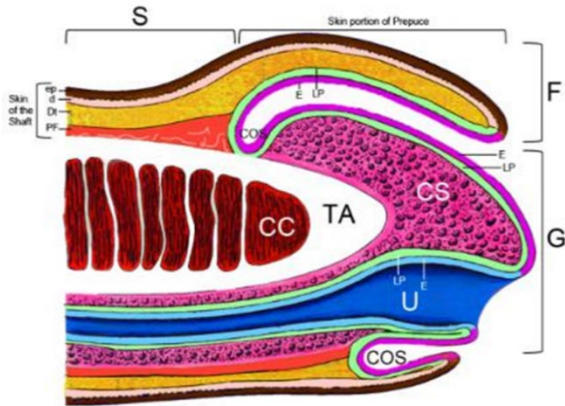

Figure 8. Anatomical Sites and Levels. Compartments: G (glans), F (foreskin), COS (coronal sulcus), S (shaft), U (urethra). Levels: E (epithelium), LP (Lamina propria), CS. (Corpus spongiosum), TA (Tunica albuginea), CC (corpus cavernosum), Dt (dartos), d (dermis), ep (epidermis), PF (penile fascia). Note the mucosal epithelium inner surface of the foreskin (in purple) in contrast with the epidermis (in brown).
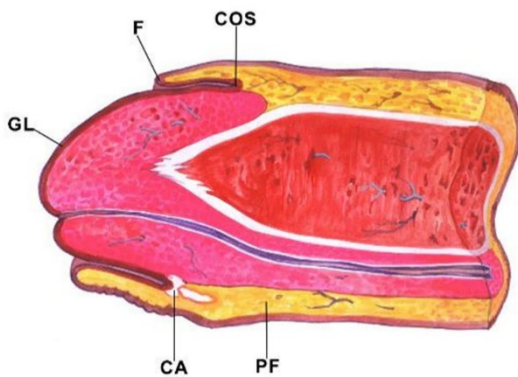

Figure 9. Tumor involving one anatomical site at the coronal sulcus (CA). GL, Glans; F, Foreskin; COS, Coronal Sulcus, PF, penile fascia.
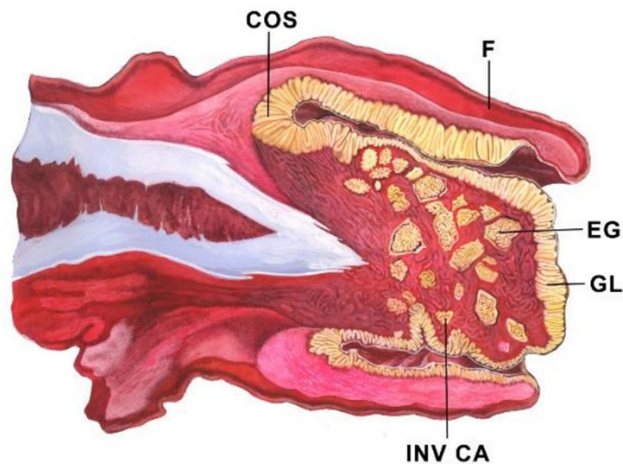
Figure 10. Tumor affecting multiple compartments. Diagrammatic representation of an exo-endophytic tumor (condylomatous-warty carcinoma) replacing the distal penis.EG, endophytic growth. Tumor involves glans (GL), coronal sulcus (COS), and foreskin inner mucosal epithelium (F).

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F. Macroscopic Features

Gross features in invasive penile carcinoma are variable but, in many cases, distinctive permitting a gross diagnosis. The most common is that of an ulcerative non-exophytic tumor mass, not infrequent is the verruciform pattern observed in a third of all cases, or a superficial flat and rarely a polypoid mass. A mixed combination of these features also occurs. The common subtype of SCC usually presents with a non-exophytic ulcerated mass whereas there are various tumor subtypes presenting as verruciform, typically the verrucous, condylomatous, and papillary NOS carcinomas. Warty carcinomas have a more uniform and homogeneous micronodular appearance whereas verrucous carcinomas show an asymmetrical larger coarser nodularity. Classical or Giant condylomas may be grossly similar to condylomatous and verrucous carcinomas. Sarcomatoid carcinomas classically present as a polypoid and or necrotic and hemorrhagic mass (Figure 11).

Cut surface on a penectomy specimen may identify special tumors. The papillomatous feature with a dark central core is characteristic of warty carcinomas (Figure 12). The sharply delineated tumor front is present in giant condylomas and verrucous carcinomas (Figure 13). The ulcerating and solid beige features with minute yellow necrotic foci is seen in basaloid carcinomas. Carcinoma cuniculatum diagnosis is made on the basis of a gross tumor burrowing pattern of growth.

Figure 11. Polypoid necrotic and hemorrhagic sarcomatoid carcinoma. In green there is viable tumor invading corpus cavernosum after destruction of the tunica albuginea.

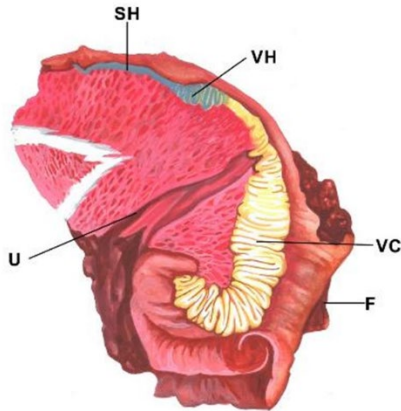**Figure 12.** Cut surface of warty (condylomatous) carcinoma involving glans and foreskin.

Figure 13. Cut surface of verrucous carcinoma (VC) of glans. VH, verrucous hyperplasia; SH, squamous hyperplasia; U, urethra; F, Foreskin.

G. Tumor Size

Gross tumor measurement in penile carcinomas may be done in three dimensions in cm but measuring the maximum diameter should suffice. The TNM staging system does not consider the size of penile tumors as an important criterion for classification. Metastasizing and non-metastasizing tumors are of similar size in some studies but not in all.[1,2] Tumors diagnosed in tropical developing countries tend to be larger and more invasive than those from northern countries indicating a higher stage at diagnosis.

The apparent lack of correlation between tumor size and nodal spread or patients' outcome may be due to the inclusion of verruciform and non-verruciform tumors as one group in the studies evaluating prognosis. Verruciform carcinomas (verrucous, papillary NOS, and warty [condylomatous]) are rarely associated with metastasis, irrespective of their size. Cuniculatum carcinoma, among the largest penile carcinomas, are not associated with regional or distant spread.[3] These neoplasms comprise at least a third of all penile tumors and are usually of large size, in fact significantly larger than other types of squamous cell carcinomas of the penis except the sarcomatoid variant. Tumor size may be a significant prognostic marker when verruciform neoplasms are excluded from the evaluation. We found no studies specifically addressing this approach of size evaluation.

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H. Histologic Subtype of Squamous Cell Carcinoma

The World Health Organization (WHO) classification of tumors of the penis was recently published.[1] Most penile cancers are squamous cell carcinomas (SCC), and most arise from the epithelium of the distal portion of the penis (including glans, coronal sulcus, and mucosal surface of the foreskin). Squamous cell carcinoma of the usual type (keratinizing SCC) comprises about 50% to 60% of all cases.[2,3,4] There are other SCC subtypes showing distinctive morphological and outcome features.[3,4,5] The different histological subtypes correlate with different rates of regional/nodal and systemic dissemination.

Squamous cell carcinoma are broadly defined as HPV-associated and HPV-independent. If ancillary studies to make that distinction are not available, "Squamous cell carcinoma NOS" can be used. The latest WHO edition aimed at simplifying the squamous cell carcinoma subtypes by grouping distinct morphologic subtypes which have similar behavior and pathogenesis, under one encompassing parent subtype. For example, pseudohyperplastic and acantholytic/ pseudoglandular patterns are eclipsed under HPV-independent squamous cell carcinoma of the usual type. Similarly, carcinoma cuniculatum is included in verrucous carcinoma. When more than one histologic pattern is present, using "mixed" subtype and specifying the different histologies is encouraged. Unusual HPV-positive poorly differentiated carcinomas with tumor-associated inflammatory cells and medullary features have been reported.[5]

Penile cancer subtypes can be prognostically stratified into three groups. The low-risk group includes verruciform tumors such as verrucous, papillary, and warty/condylomatous carcinomas.[6,7] More recently described histologic patterns, such as pseudohyperplastic and carcinoma cuniculatum of the penis, also belong to this category of excellent prognosis.[8,9]The high-risk category is comprised of basaloid, sarcomatoid, adenosquamous, and poorly differentiated SCC of the usual type.[10,11,12]There is an intermediate category of metastatic risk that includes most SCCs of the usual type, some mixed neoplasms (such as hybrid verrucous carcinomas), and high-grade variants of warty/condylomatous carcinomas.[7]

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I. Verruciform Tumors (special consideration)

Verruciform neoplasms of the penis are a heterogenous group of benign or low-grade malignant exophytic tumors representing about a third of all penile malignant tumors and due to confusing older literature, most problematic to diagnose. Some of them are non-HPV related and others are HPV related. They are Verrucous carcinoma, warty (condylomatous) carcinoma, papillary carcinoma NOS and typical and giant condylomas (Buschke-Lowenstein tumor) and their mixtures or variants. The differential diagnosis may be challenging to the inexperienced pathologist but there are distinctive features to help delineate in Figure 14.
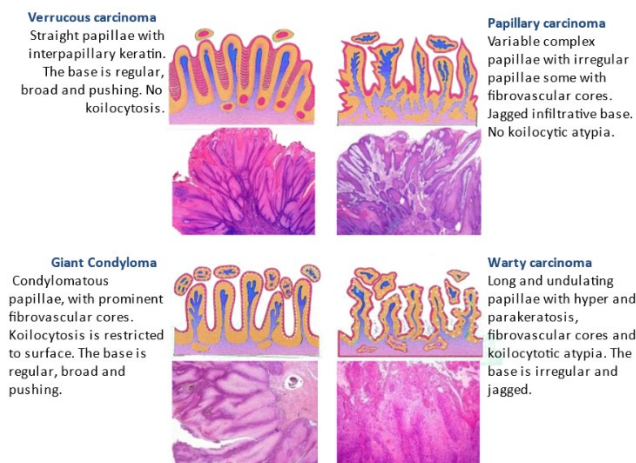

Figure 14. Verruciform tumors: Diagrammatic representation and histology of common verruciform tumors.

J. Histologic Grade

Histological grade has been consistently reported as an influential predictive factor of groin metastasis and dissemination of penile cancer.[1,2,3] We recommend a method to grade penile SCCs as follows:

- **Grade 1** is an extremely well-differentiated carcinoma, with a minimal deviation from the morphology of normal/hyperplastic squamous epithelium.
- **Grade 2** tumors show a more disorganized growth as compared to grade 1 lesions, higher nuclear-to-cytoplasmic ratio, evident mitoses, and, although present, less prominent keratinization.
- **Grade 3** are tumors showing any proportion of anaplastic cells, identified as solid sheets or irregular small aggregates, cords or nests of cells with little or no keratinization, high nuclear-to-cytoplasmic ratio, thick nuclear membranes, nuclear pleomorphism, clumped chromatin, prominent nucleoli, and numerous mitosis.[3,4]

A tumor should be graded according to the least differentiated component. Any proportion of grade 3 should be noted in the report.[4]

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K. Thickness/Depth of Invasion

The tumor depth in small lesions is best obtained by perpendicularly sectioning along the tumor's central axis. For large glans tumors, it is preferred to section the specimen longitudinally in half, with additional parallel sections of each half, using as an axis the central and ventral penile urethra. The depth of invasion of SCC is defined as a measurement in millimeters from the epithelial-stromal junction of the adjacent nonneoplastic epithelium to the deepest point of invasion. In larger tumors, especially verruciform ones, the previously mentioned system is not applicable, and we measure the thickness from the surface (excluding the keratin layer) to the deepest point of invasion (Figure 15). Depth of invasion and tumor thickness are of equivalent significance.

There is a correlation between depth of invasion and outcome in penile cancers. Minimal risk for metastasis was reported for tumors measuring less than 5 mm in thickness.[1,2]Tumors invading deeper into penile anatomical levels are usually associated with a higher risk for nodal involvement. There is also a correlation between deeper infiltration and higher histological grade, although some exceptions do occur.[3]Tumors invading corpus cavernosum are at higher risk for nodal metastases than those invading only corpus spongiosum,[3,4] and the deepest erectile tissue invaded should be clearly stated in the final pathology report. Per AJCC 8 edition, tumor invading into subepithelial connective tissue (lamina propria), Dartos muscle, and Buck's fascia is staged as T1; tumor invading into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion is staged as T2; tumor invading into corpora cavernosum (including tunica albuginea) with or without urethral invasion is staged as T3; and tumor invading into adjacent structures (i.e., scrotum, prostate, pubic bone) is staged as T4.
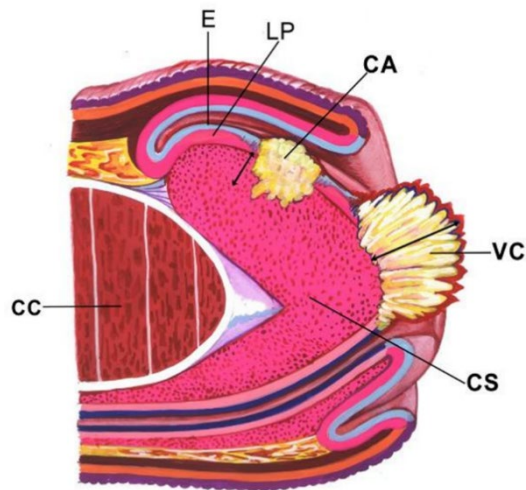
Figure 15. Methods for measurement for non-verruciform and verruciform tumors. CA represents depth of invasion in a usual squamous cell carcinoma invading corpus spongiosum (CS). VC represents thickness of a verrucous carcinoma (VC) with a broadly based invasive front. CC, corpus cavernosum.

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L. Tumor Base of Infiltration
Two patterns are recognized: infiltrating (invasion in blocks of small solid strands of cell tumors broadly infiltrating the stroma) and pushing infiltration (tumor cells invading in large cell blocks with well-defined tumor-stroma interface). The infiltrating pattern of invasion is associated with a higher risk for nodal involvement.[1]

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M. Tumor Deep Borders
There has been some confusion in the reporting of the deep border of invasion or tumor front. Along the staging models, terminologies were not always sufficiently clear to communicate pathological facts. This resulted in a lack of precision and consensus in the definition of terms such as invasive vs. non-invasive and localized vs. non-localized cancers. With the purpose of clarification, we are suggesting four features

or patterns of tumor growth and invasion in relation to current staging[1]: 1. Non-invasive, 2. Invasive, broadly-based non-destructive, 3. Invasive, destructive but well-delineated front en bloc, 4. Invasive, destructive, irregular, finger-like front.

1. Non-invasive neoplasm: it is a tumor growing above the level of the squamous epithelium, sparing lamina propria of glans, coronal sulcus, and foreskin or shaft dermis (Figure 16 A). A non-invasive neoplasm is like an in situ lesion but is especially applied to exophytic or bulkier clinically evident tumor growing above the level of the basal cell layer. All lesions growing at or above the level of the basal epithelium are staged as pTa.

2. Invasive (localized) neoplasm with a broadly-based pushing tumor front: the tumor grows into lamina propria or corpus spongiosum or deeper, it is solid without separated nests and the interface between neoplasm and stroma is regular and broadly based. The growth may be in ample sheets or in scalloped undulating borders (Figure 16 B). Whereas there was some disagreement in the nomenclature of broadly-based tumors being invasive or non-invasive, most of our colleagues now consider broadly-based invasion to any tumor growing beyond the limits of the basal layer squamous epithelia into lamina propria. What is clinically important is the fact that differentiated tumors either non-invasive (in situ) or invasive but with a sharply delineated broadly-based tumor front have no risk of regional metastasis. Applying strictly current terminology these broadly-based but invasive tumors should be staged at least as pT1 and/or according to their anatomical level of invasion, which in case of verrucous carcinomas may be quite deep. However, analogically to bladder pTa tumors pushing into lamina propia with a broad-base, these rare tumors may still be considered, albeit technically invasive, as localized. It is our opinion that since they have no metastatic potential, independent of their level of invasion, they should be classified as pTa.

3. Invasive neoplasm with a destructive irregular front but en bloc, well-delineated margins: Front of invasion is not broadly-based but destructive, albeit there is a well-delineated border between tumor and stroma (Figure 16 C). Lamina propria and deeper anatomical levels are compromised. This pattern of invasion, described by Aita et al was found to be associated with better prognosis comparing with irregular finger-like invasion.[2] It is validated and it is part of a recently proposed predictive scoring index for penile cancer.[3,4] Tumors with these features are staged as at least pT1.

4. Invasive neoplasm with an irregular/destructive finger-like tumor front: the limits of tumor and the stroma are irregular, destructive, finger-like. Lamina propria or deeper anatomical levels are compromised by the tumors (Figure 16 D). Tumors in this stage of invasion are classified as at least pT1.
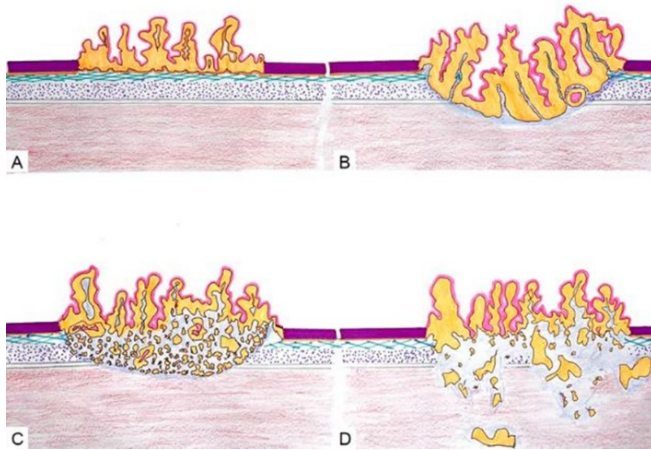
Figure 16. Patterns of invasion. Non-invasive neoplasm (A). Invasive (localized) (B) neoplasm with a broadly-based pushing tumor front. Invasive neoplasm with a destructive irregular front but en bloc, well-delineated margins (C). Invasive neoplasm with an irregular/destructive finger-like tumor front (D).

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N. Tumor Extent
The anatomy of the penis is complex and there are distinctive anatomical sites with variable tissue layers composition.[1] Tumors may in an exclusive manner originate in the glans, the foreskin, the coronal sulcus or the shaft, in this order of frequency. Not uncommonly, especially in specimens from patients from southern tropical countries, large tumors involve more than one site. Superficially spreading carcinomas may horizontally grow affecting more than one site (Figure 17).[2] Tumors of the foreskin tend to be better differentiated and associated with lichen sclerosus, carrying a better prognosis than those exclusive of the glans. For this reason, is recommended to evaluate tumor extension according to separate anatomical sites.

In the glans, tissue layers for tumor invasion are lamina propria, corpus spongiosum, tunica albuginea and corpus cavernosum. The tunica is part of the corpus cavernosum. In the foreskin the layers are lamina propria, dartos and skin (dermis and epidermis) (Figure 18).[1] In the shaft, a recent evaluation of primary tumors exclusive of this site observed the following layers in relation to tumor invasion: skin, dartos, penile (Buck) fascia, tunica albuginea and corpus cavernosum (Figure 19).[3] Tumors primary at the sulcus are very rare and we did not find a histological evaluation of tumor invasion of this site according to anatomical layers.
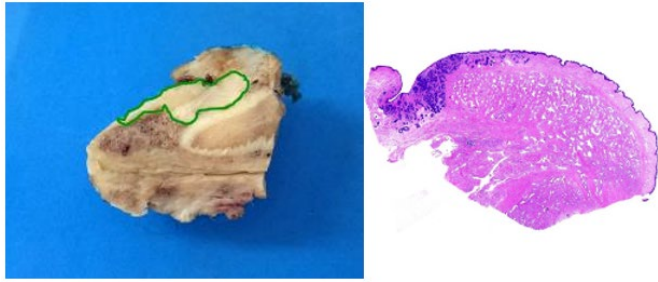
Figure 17. Tumor extension. Extension of tumor (in green) from glans to penile fascia (A). Lamina propria spread (B): Tumor growths along the lamina propria in glans, coronal sulcus and foreskin.
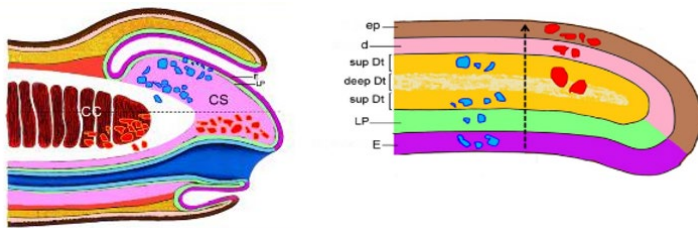

Figure 18. Extent, anatomical levels of invasion. Carcinomas of Glans: Each spot represents one case invading a specific anatomical level. Cases above the broken horizontal line (in blue) had negative inguinal nodes. Cases below the line (in red) had positive nodes. Carcinomas exclusive of the Foreskin: Tumor invasion is from inner mucosa to skin (arrow). Blue and red spots indicate tumor deepest invasion point by anatomical level.
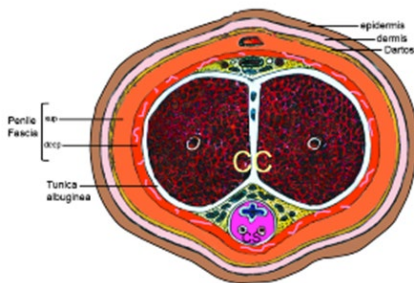

Figure 19. Cross section of penile shaft. Anatomical levels from Surface to Deep: epidermis, dermis, dartos, penile (Buck) fascia, tunica albuginea and corpus cavernosum.

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O. Lymphatic and/or Vascular Invasion
Vascular invasion, lymphatic or venous, adversely affects prognosis of penile cancer.[1,2,3,4,5] The TNM staging classification in the 8th edition of the AJCC Cancer Staging Manual subdivides T1 tumors into

T1a and T1b based on the absence or presence of lymphatic and/or vascular invasion or poorly differentiated tumors.[6] Embolic involvement of lymphatic vascular spaces occurs usually near the invasive tumor front, but it may also be found at a certain distance from the primary tumor in anatomical areas such as the lamina propria, penile fascia, and especially in the subepithelial connective tissues surrounding penile urethra. Venous invasion indicates a more advanced stage of the disease and is related to the compromise of the specialized erectile venous structures of corpora spongiosa and cavernosa.

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P. Nomograms, Risk Groups, and Perineural Invasion
An evaluation of clinical and pathological variables using a nomogram was recently developed.[1] The selected factors were clinical stage of lymph nodes, microscopic growth pattern, grade, vascular invasion, and invasion of corpora spongiosa and cavernosa and urethra. The probability of nodal metastasis as predicted by the nomogram was close to the real incidence of metastasis observed at follow-up. A second nomogram to estimate predictions of survival at 5 years with the same clinical and pathological factors gave similar results.[2]

More recently, perineural invasion and histological grade were found to be the strongest independent predictors of mortality in penile tumors 5 to 10 mm thick. A nomogram considering the predictive value of perineural invasion and histological grade was accordingly constructed.[3] Risk groups stratification systems are available to predict the likelihood of inguinal nodal involvement and for therapeutic planning and are based on a combination of histological grade and pT stage.[4,5,6,7] Strongest predictive power results from the combination of histological grade, deepest anatomical level of infiltration, and presence of perineural invasion. These factors are used for constructing the prognostic index.[8]

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Q. Resection Margins

Positive margins adversely affect prognosis in patients with penile squamous cell carcinomas.[1,2,3] Important margins to be examined in partial penectomy specimens include: (1) proximal urethra and surrounding periurethral cylinder consisting of epithelium, subepithelial connective tissue (lamina propria), corpus spongiosum, and penile fascia; (2) proximal shaft with corresponding corpora cavernosa separated and surrounded by the tunica albuginea and Buck's fascia; and (3) skin of shaft with underlying corporal dartos[4] (Figure 20 and 21). The coronal sulcus mucosal margin and cutaneous margin should be entirely examined when evaluating circumcision specimens.
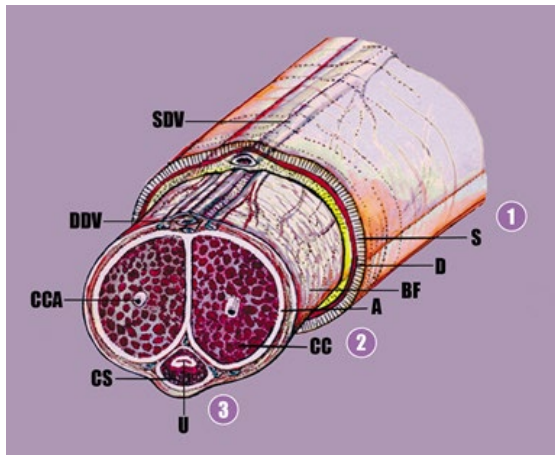

Figure 20. Partial penectomy specimen; anatomical structures of proximal resection margin. The ventral urethra (U) is surrounded by the corpus spongiosum (CS) and a delicate white tunica albuginea (A). The latter is also surrounding the corpora cavernosa (CC). The penile fascia (Buck's fascia) (BF) is located underneath skin (S) and dartos (D). The proximal margin of resection should be cut en face and all the structures including the entire circumference of the urethra with periurethral cylinder should be examined.The 3 important margins to be examined include (1) skin of the shaft with underlying dartos and penile fascia, (2) the corpora cavernosa with surrounding tunica albuginea, and (3) the urethra and periurethral cylinder that includes the lamina propria, corpus spongiosum, albuginea, and penile fascia. Abbreviations: CCA, cavernous artery; DDV, deep dorsal vein; SDV, superficial dorsal vein.
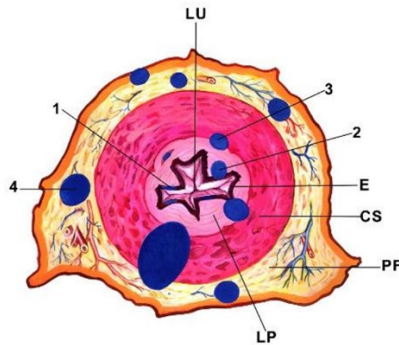
Figure 21. Urethral margin. Common sites of positive urethral margin of resection are indicated by the blue dots: 1. Intraepithelial, 2. lamina propria, 3. lymphatic vessels-corpus spongiosum and 4. Penile fascia. LU, lumen; E, epithelium; CS: corpus spongiosum; PF, penile fascia.

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R. Number of Involved Lymph Nodes and Extension of the Lymphadenectomy

The presence of more than two positive lymph nodes in one inguinal basin increases the likelihood of contralateral inguinal and ipsilateral pelvic nodal involvement.[1] In such cases, prophylactic contralateral inguinal and ipsilateral pelvic lymphadenectomy is advised. Any pelvic lymph node involvement or extracapsular extension of any regional lymph node (inguinal or pelvic) is staged N3. The number and percentage of positive nodes involved also has an impact on survival.[2,3]

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S. Distant Metastasis

Penile carcinoma is a potentially lethal disease. It is considered a loco-regional disease in early stages but wide dissemination may occur. Liver, heart, lungs, and non-regional lymph nodes are the most common sites of involvement at autopsy.[1] Notoriously, the heart is a common site of penile cancer metastasis (Figure 22).[2,3]

Figure 22. Sites of metastasis in an autopsy study of 14 patients. Liver, heart, and lungs are the most common sites.

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T. TNM Staging Classification
The protocol recommends the use of the TNM staging system of the American Joint Committee on Cancer (AJCC) for carcinoma of the penis.[1] By AJCC convention, the designation T refers to a primary tumor that has not been previously treated. The symbol p refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or a biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesion. Pathologic staging is usually performed after surgical resection of the primary tumor. The summary of changes in the TNM staging classification in the 8th edition of the AJCC Cancer Staging Manual is as follows:

Change	Details of Change
Histologic Grade (G)	The 3-tiered World Health Organization (WHO)/International Society of Urological Pathology (ISUP) grading system has been adopted. Any proportion of anaplastic cells is sufficient to categorize a tumor as grade 3.
Definition of Primary Tumor (T)	Ta definition is now broadened to include noninvasive localized squamous carcinoma.
Definition of Primary Tumor (T)	T1a and T1b have been separated by an additional prognostic indicator-the presence or absence or perineural invasion.

Change	Details of Change
Definition of Primary Tumor (T)	T1a or T1b are described by the site where they occur on the penis and are designated glans, foreskin, or shaft. Anatomic layers invaded are described for the three locations.
Definition of Primary Tumor (T)	T2 definition includes corpus spongiosum invasion.
Definition of Primary Tumor (T)	T3 definition now involves corpora cavernosum invasion.
Definition of Regional Lymph Nodes (N)	pN1 is defined as ≤2 unilateral inguinal metastases, no extranodal extension.
Definition of Regional Lymph Nodes (N)	pN2 is defined as ≥3 unilateral inguinal metastases or bilateral metastases.

Additional Descriptor

The m suffix indicates the presence of multiple primary tumors and is recorded in parentheses, e.g., pTa(m)N0M0.

Anatomic Stage/Prognostic Groups

Group	T	N	M
Stage 0is	Tis	N0	M0
Stage 0a	Ta	N0	M0
Stage I	T1a	N0	M0
Stage IIA	T1b	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T1-3	N1	M0
Stage IIIB	T1-3	N2	M0
Stage IV	T4	Any N	M0
Stage IV	Any T	N3	M0
Stage IV	Any T	Any N	M1

Prognostic Factors (Site-Specific Factors)

Factors required for staging: None

Clinically significant factors:

- Involvement of corpus spongiosum
- Involvement of corpus cavernosum
- Percentage of tumor that is poorly differentiated
- Verrucous carcinoma depth of invasion
- Size of largest lymph node metastasis
- Extranodal/extracapsular extension
- Human papillomavirus (HPV) status

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U. Penile Intraepithelial Neoplasia

Penile Intraepithelial Neoplasia (PeIN), is more common than invasive cancers in countries of low incidence for penile cancer.[1] It is classified as HPV-associated and HPV-independent.[2] Various HPV-related patterns were described, most typically basaloid, warty, and mixed warty basaloid. HPV-independent PeIN is represented by the Differentiated type. Most patterns can be recognized with routine

H&E stains except in some cases where immunohistochemistry is helpful (see below). HPV 16 is the most common genotype but others may be present, especially in warty PeIN. HPV-associated lesions are not uncommonly multicentric[3] and they affect preferentially the glans but foreskin and skin of the shaft may also be involved. More than one pattern may be present in the same lesion or in the same specimen (hybrid HPV-associated PeIN) and occasionally HPV-associated and HPV-independent PeIN may be found in the same specimen.[4] HPV16 is more prevalent in basaloid than in warty PeIN.[5]

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V. Special Studies/Ancillary Tests

Immunohistochemical stains and molecular studies are non-required elements for all cases. In clinical practice a panel of p16 and Ki67 may be useful to determine the profile of penile intraepithelial neoplasia variants and as an aid in the differential diagnosis of squamous hyperplasia versus differentiated PeIN, and non-HVP versus HPV subtypes of PeIN.[1] Ki67 positive cells remain at the basal layer in squamous hyperplasia and are above this level in differentiated PeIN. P16 stain is negative in keratinizing pleomorphic variants of PeIN which may simulate HPV-related PeIN, which are p16 positive. P16 is also used as a surrogate for HPV to distinguish HPV from non-HPV invasive neoplasms.[2] The 2016 and 2022 WHO and the 2020 AFIP classifications of invasive penile squamous carcinoma separates non-HPV from HPV-related tumors. The majority of these neoplasms can be recognized using routine pathology staining, but pathologists should be familiar with the heterogeneous albeit distinctive morphological patterns of HPV-related tumors. P16 immunostaining can be used in difficult cases.

Molecular techniques such as in situ hybridization or, ideally, PCR are used for HPV detection mostly in research studies. There are few reports on the practical value to establish molecular practices as mandatory and some of them are not available in many laboratories, especially those in developing countries.[3,4]

HPV genotyping may be necessary for the differential diagnosis of giant or atypical condylomas and warty (condylomatous) carcinomas. In such controversial cases, histologically similar tumors may be classified as condyloma or carcinoma according to the respective presence of low or high-risk HPV genotypes. There is a considerable recent molecular pathology literature, some based on possible targeted therapies, but most are at an experimental level.[5,6,7,8,9,10] For the time being these data are in the research area.

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