



cap

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

Protocol applies to primary carcinoma of the penis. Primary urethral carcinomas and melanomas are not included.

Based on AJCC/UICC TNM, 7th edition

Protocol web posting date: October 2013

Procedures

- Incisional biopsy
- Excisional biopsy
- Partial penectomy
- Total penectomy
- Circumcision

Authors

Elsa F. Velazquez, MD*

Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston MA

Mahul B. Amin, MD

Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California

Jonathan I. Epstein, MD

Department of Pathology, Johns Hopkins Hospital, Baltimore, Maryland

David J. Grignon, MD

Department of Pathology, Indiana University, Indianapolis, Indiana

Peter A. Humphrey, MD, PhD

Department of Pathology and Immunology, Washington University School of Medicine and Barnes-Jewish Hospital, St. Louis, Missouri

Curtis A. Pettaway, MD

Department of Urology, University of Texas MD Anderson Cancer Center, Houston, Texas

Andrew A. Renshaw, MD

Department of Pathology, Baptist Hospital of Miami, Miami, Florida

Victor E. Reuter, MD

Pathology Department, Memorial Sloan-Kettering Cancer Center, New York, New York

John R. Srigley, MD

Department of Laboratory Medicine, Credit Valley Hospital, Mississauga, Ontario, Canada

Ming Zhou, MD, PhD

Department of Pathology, New York University Langone Medical Center, New York, New York

Antonio L. Cubilla, MD†

Department of Pathology, National University of Asuncion and Instituto de Patologia e Investigacion, Asuncion, Paraguay

For the Members of the Cancer Committee, College of American Pathologists

* Denotes primary author. † Denotes senior author. All other contributing authors are listed alphabetically.

© 2013 College of American Pathologists (CAP). All rights reserved.

The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the Protocols solely for their individual use in reporting on surgical specimens for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) **Dictation** from the original or modified protocols for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) **Copying** from the original or modified protocols into a text-based patient record on paper, or in a word processing document; (3) The use of a **computerized system** for items (1) and (2), provided that the protocol data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the Protocols in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from the CAP.

Any public dissemination of the original or modified protocols is prohibited without a written license from the CAP.

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the "Surgical Pathology Cancer Case Summary" portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.

CAP Penis Protocol Revision History

Version Code

The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Penis 3.2.0.0

Summary of Changes

The following changes have been made since the February 2011 release.

Title Page

The subtitle was expanded to exclude primary urethral carcinomas and melanomas.

Entire Protocol

“Lamina propria” was replaced with “subepithelial connective tissue (lamina propria)”

Incisional Biopsy, Excisional Biopsy, Partial Penectomy, Total Penectomy, Circumcision

Tumor Type

A reporting element for tumor type was added, as follows:

Tumor Type

- Invasive carcinoma
- Noninvasive carcinoma
- Carcinoma in situ

Microscopic Tumor Extension

Anatomic Levels

For each anatomic level:

- “Noninvasive” was added as a selectable element
- “Not applicable” was deleted

Additional Pathologic Findings

Penile intraepithelial neoplasia (PeIN) was updated, as follows:

- + Penile intraepithelial neoplasia (PeIN)
 - + Differentiated (simplex)
 - + Squamous intraepithelial lesion, grade 1
 - + Squamous intraepithelial lesion, grade 2
 - + Other (specify): _____

Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

PENIS: Incisional Biopsy, Excisional Biopsy, Partial Penectomy, Total Penectomy, Circumcision**Select a Single Response Unless Otherwise Indicated.****Procedure**

- Incisional biopsy
 Excisional biopsy
 Partial penectomy
 Total penectomy
 Circumcision
 Other (specify): _____
 Not specified

Foreskin (presence and type) (select all that apply) (Note A)

- Present (uncircumcised)
 - + Short
 - + Medium
 - + Long
 - + Phimotic Not identified (circumcised)
 Cannot be determined

Lymphadenectomy

- Not applicable
 Sentinel node biopsy
 Inguinal (superficial and deep)
 External iliac
 Internal iliac
 Pelvic nodes
 Other (specify): _____

Lymph Node Sampling (Note B)

- No nodes submitted or found

Number of Lymph Nodes Examined

- Specify: _____
 Number cannot be determined (explain): _____

Number of Lymph Nodes Involved

- Specify: _____
 Number cannot be determined (explain): _____

Specimen Size

Specify: ___ x ___ x ___ cm

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Tumor Site (if multiple sites are involved, select all that apply)

- Glans
- Foreskin mucosal surface
- Foreskin skin surface
- Coronal sulcus (balanopreputial sulcus)
- Skin of the shaft
- Penile urethra

Tumor Size

- Greatest dimension: ___ cm
 + Additional dimensions: ___ x ___ cm

+ Tumor Focality

- + Unicentric
- + Multicentric

+ Tumor Macroscopic Features (select all that apply)

- + Flat
- + Ulcerated
- + Polypoid
- + Verruciform
- + Necrosis
- + Hemorrhage
- + Other (specify): _____

+ Tumor Deep Borders (select all that apply) (Note C)

- + Pushing (broadly base)
- + Infiltrative (jagged)
- + Other (specify): _____

+ Macroscopic Extent of Tumor (select all that apply)

- + In the glans:
 - + Tumor involves subepithelial connective tissue (lamina propria)
 - + Tumor involves corpus spongiosum
 - + Tumor involves tunica albuginea
 - + Tumor involves corpus cavernosum
 - + Tumor involves distal (penile) urethra
 - + Not applicable
- + In the foreskin:
 - + Tumor involves subepithelial connective tissue (lamina propria)
 - + Tumor involves dartos
 - + Tumor involves preputial skin
 - + Not applicable

- + In the shaft:
- + ___ Tumor involves skin
- + ___ Tumor involves dartos
- + ___ Tumor involves Buck's fascia
- + ___ Tumor involves corpus spongiosum
- + ___ Tumor involves corpus cavernosum
- + ___ Tumor involves proximal urethra
- + ___ Not applicable

Macroscopic Assessment of Resection Margins (select all that apply)

- ___ Cannot be assessed
- ___ Grossly uninvolved
- ___ Grossly involved (specify for penectomy or circumcision specimen below)

For penectomy specimens:

- ___ Urethral
- ___ Periurethral tissues (subepithelial connective tissue (lamina propria), corpus spongiosum, Buck's fascia)
- ___ Corpora cavernosa
- ___ Buck's fascia at penile shaft
- ___ Skin
- ___ Other (specify): _____

For circumcision specimens:

- ___ Coronal sulcus margin
- ___ Cutaneous margin

Tumor Type

- ___ Invasive carcinoma
- ___ Noninvasive carcinoma
- ___ Carcinoma in situ

Histologic Type (select all that apply) (Note D)

- ___ Squamous cell carcinoma (SCC)
 - ___ Usual (keratinizing)
 - ___ Basaloid
 - + ___ Warty (condylomatous)
 - ___ Verrucous
 - + ___ Cuniculatum
 - + ___ Papillary, not otherwise specified (NOS)
 - ___ Sarcomatoid
 - + ___ Pseudohyperplastic
 - + ___ Acantholytic (pseudoglandular)
 - + ___ Mixed SCCs
 - ___ Adenosquamous
- ___ Primary neuroendocrine carcinoma
- ___ Paget's disease
- ___ Adnexal carcinoma (specify type): _____
- ___ Clear cell carcinoma
- ___ Carcinoma, type cannot be determined
- ___ Other (specify): _____

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Histologic Grade (Note E)

- Not applicable
- GX: Cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated

Microscopic Tumor Extension (select all that apply)Anatomical Levels

In the glans:

- Noninvasive
- Tumor involves subepithelial connective tissue (lamina propria)
- Tumor involves corpus spongiosum
- Tumor involves tunica albuginea
- Tumor involves corpus cavernosum

In the coronal sulcus:

- Noninvasive
- Tumor involves subepithelial connective tissue (lamina propria)
- Tumor involves dartos
- Tumor involves Buck's fascia

In the foreskin:

- Noninvasive
- Tumor involves subepithelial connective tissue (lamina propria)
- Tumor involves dartos
- Tumor involves preputial skin

In the shaft:

- Noninvasive
- Tumor involves skin
- Tumor involves dartos
- Tumor involves Buck's fascia
- Tumor involves corpus spongiosum
- Tumor involves corpus cavernosum

Other Extension

- Penile (distal) urethra
- Proximal urethra
- Prostate
- Scrotum
- Regional skin (pubis, inguinal)

+ Tumor Thickness/Depth (Note F)

+ Specify: ___ mm

Margins of Resection (select all that apply) (Note G)

- Cannot be assessed
 Histologically uninvolved
 Histologically involved (specify for penectomy or circumcision specimens below):

For penectomy specimens:

- Urethral
 Periurethral tissues (subepithelial connective tissue [lamina propria], corpus spongiosum, Buck's fascia)
 Corpus cavernosum
 Buck's fascia at penile shaft
 Skin
 Other (specify): _____

For circumcision specimens:

- Coronal sulcus margin
 Cutaneous margin

Lymph-Vascular Invasion (Note H)

- Not identified
 Present
 Indeterminate

Perineural Invasion (Note I)

- Not identified
 Present
 Indeterminate

Pathologic Staging (pTNM)¹ (Note J)

TNM Descriptors (required only if applicable) (select all that apply)

- m (multiple primary tumors)
 r (recurrent)
 y (posttreatment)

Primary Tumor (pT)

- pTX: Primary tumor cannot be assessed
 pT0: No evidence of primary tumor
 pTis: Carcinoma in situ
 pTa: Noninvasive verrucous carcinoma[#]
 pT1a: Tumor invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (ie, grade 3-4)
 pT1b: Tumor invades subepithelial connective tissue with lymph vascular invasion or is poorly differentiated
 pT2: Tumor invades corpus spongiosum or cavernosum
 pT3: Tumor invades urethra
 pT4: Tumor invades other adjacent structures

[#] Broad pushing penetration (invasion) is permitted, but destructive invasion argues against this diagnosis.

⁺ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Regional Lymph Nodes (pN)

- pNX: Regional lymph nodes cannot be assessed
- pN0: No regional lymph node metastasis
- pN1: Metastasis in a single inguinal lymph node
- pN2: Metastasis in multiple or bilateral inguinal lymph nodes
- pN3: Extranodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral

Distant Metastasis (pM)

- Not applicable
- pM1: Distant metastasis#

Lymph node metastasis outside of the true pelvis in addition to visceral or bone sites.

+ Additional Pathologic Findings (select all that apply) (Note K)

- + None identified
- + Penile intraepithelial neoplasia (PeIN)
 - + Differentiated (simplex)
 - + Squamous intraepithelial lesion, grade 1
 - + Squamous intraepithelial lesion, grade 2
 - + Other (specify): _____
- + Lichen sclerosus
- + Squamous hyperplasia
- + Condyloma acuminatum
- + Other (specify): _____

+ Ancillary Studies

- + Specify: _____
- + Not performed

+ Comment(s)

Explanatory Notes

A. Types of Foreskin

There are 3 foreskin types: 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.² Phimosis is present in up to one-half of patients with penile carcinoma,² and its presence is considered a risk factor for the development of this tumor.³⁻⁵

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

The presence of more than 2 positive lymph nodes in 1 inguinal basin increases the likelihood of contralateral inguinal and ipsilateral pelvic nodal involvement.⁶ In such cases, prophylactic contralateral inguinal and ipsilateral pelvic lymphadenectomy is advised. The number and percentage of positive nodes involved also has an impact on survival.^{7,8}

C. 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.⁹

D. Histological Subtype of Squamous Cell Carcinoma

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 prepuce). Squamous cell carcinoma of the usual type (keratinizing SCC) comprises about 50% to 60% of all cases.¹⁰⁻¹² There are other SCC variants showing distinctive morphological and outcome features.¹⁰⁻¹² The different histological subtypes correlate with different rates of regional/nodal and systemic dissemination. Penile cancer subtypes can be prognostically stratified in 3 groups. The low-risk group includes verruciform tumors such as verrucous, papillary, and warty/condylomatous carcinomas.^{13,14} More recently described subtypes, such as pseudohyperplastic and carcinoma cuniculatum of the penis, also belong to this category of excellent prognosis.^{15,16} The high-risk category is comprised by basaloid, sarcomatoid, adenosquamous, and poorly differentiated SCC of the usual type.¹⁷⁻¹⁹ 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.¹⁴

E. Histological Grade

Histological grade has been consistently reported as an influential predictive factor of groin metastasis and dissemination of penile cancer.²⁰⁻²² 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.^{22,23}

A tumor should be graded according to the least differentiated component. Any proportion of grade 3 should be noted in the report.²³

F. Depth of Invasion

The tumor depth in small lesions is best obtained by perpendicularly sectioning along the tumor central axis. For large glans tumors, we 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. 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.^{22,24} 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.²⁵ Tumors invading corpus cavernosum are at higher risk for presenting nodal metastases than those invading only corpus spongiosum,^{26,27} and the deepest erectile tissue invaded should be clearly stated in the final pathology report.

G. Resection Margins

Positive margins adversely affect prognosis in patients with penile squamous cell carcinomas.^{10,12,28} 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 dartos²⁸ (Figure 1). The coronal sulcus margin and cutaneous margin should be entirely examined when evaluating circumcision specimens.

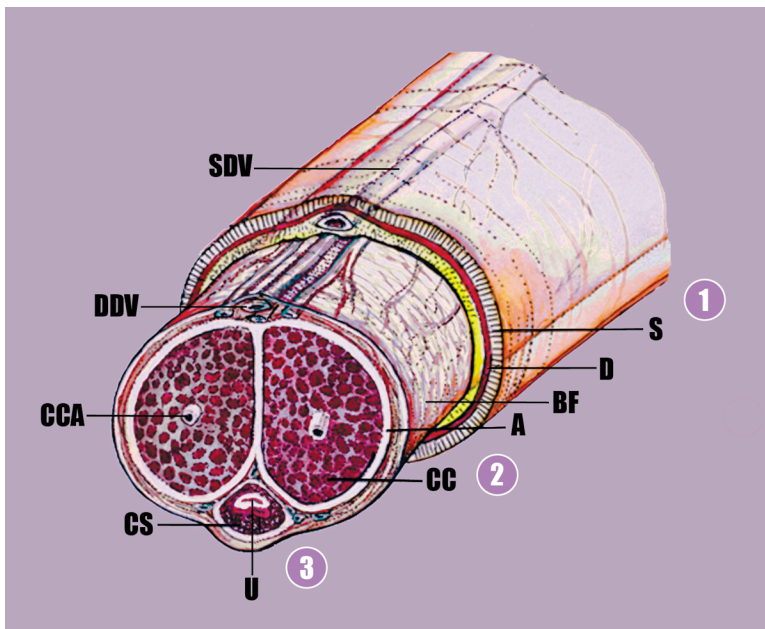


Figure 1. Partial penectomy specimen; anatomical structures of proximal resection margin. The ventral urethra (U) is surrounded by the corpus spongiosum (CS) and a delicate white tunica albuginea (A). The latter is also surrounding the corpora cavernosa (CC). The penile fascia (Buck's fascia) (BF) is 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.

H. Lymph-Vascular Invasion

Vascular invasion, lymphatic or venous, adversely affects prognosis of penile cancer.²⁹⁻³³ The new TNM staging classification in the seventh edition of the *AJCC Cancer Staging Manual*¹ subdivides T1 tumors into T1a and T1b based on the absence or presence of lymphovascular invasion or poorly differentiated tumors. 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.

I. Nomograms, Risk Groups, and Perineural Invasion

An evaluation of clinical and pathological variables using a nomogram was recently developed.³¹ 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.³² 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.²² Risk groups stratification systems are available to predict the likelihood of inguinal nodal involvement and therapeutic planning and are based on a combination of histological grade and pT stage.³⁴⁻³⁷ Strongest predictive power is given by the combination of histological grade, deepest anatomical level of infiltration, and presence of perineural invasion. These factors are used for constructing the Prognostic Index.²⁷

J. TNM Staging Classification

The protocol recommends the use of the TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) for carcinoma of the penis.¹ By AJCC/UICC 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 seventh edition of the *AJCC Cancer Staging Manual*¹ is as follows:

- T1 has been subdivided into T1a and T1b based on the presence or absence of lymphovascular invasion or poorly differentiated cancers.
- T3 category is limited to urethral invasion and prostatic invasion is now considered T4.
- Nodal staging is divided into both clinical and pathologic categories.
- The distinction between superficial and deep inguinal lymph nodes has been eliminated.
- Stage II grouping includes T1bN0M0# as well as T2-3N0M0.

M0 is defined as no distant metastasis.

Additional Descriptor

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

Anatomic Stage/Prognostic Groups

Group	T	N	M
Stage 0	Tis	N0	M0
	Ta	N0	M0
Stage I	T1a	N0	M0
Stage II	T1b	N0	M0
	T2	N0	M0
	T3	N0	M0
Stage IIIa	T1-3	N1	M0
Stage IIIb	T1-3	N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	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

K. Penile Intraepithelial Neoplasia

Penile Intraepithelial Neoplasia (PeIN) may be subclassified as differentiated (simplex), warty, basaloid, and warty/basaloid (mixed).^{38,39} Differentiated PeIN shows parakeratosis, epithelial thickening, elongation of rete ridges, prominent bridges, basal cell atypia, enlarged nuclei, and prominent nucleoli. Differentiated PeIN is frequently associated with lichen sclerosus. It is considered HPV-unrelated, there is no koilocytosis, and p16 immunohistochemical staining results (surrogate of high risk types of HPV) are usually negative. Basaloid PeIN is characterized by a replacement of the normal epithelium by small, uniform cells with round nuclei and scant cytoplasm. Numerous mitosis and apoptotic cells are usually present. Warty PeIN shows a spiky surface with parakeratosis. The normal epithelium is replaced by markedly pleomorphic cells showing prominent koilocytosis. Mixed warty-basaloid lesions are not infrequent. Warty and basaloid PeIN are HPV-related lesions and usually over-express p16.

L. Handling of the Specimen

Circumcision specimen: 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 a cardboard. Fix for several hours in formalin. Cut vertically the whole specimen labeling from 1 to 12, clockwise.

Penectomy specimen: 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 1 or more of these anatomical compartments).⁴⁰ If present, classify the foreskin as short, medium, long, and/or phimotic.² Cut the proximal margin of resection en face making sure to include the entire circumference of the urethra (Figure 1). If the urethra has been retracted, it is important to identify its resection margin and submit it entirely. The resection margin can be divided in 3 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 1). The urethra and periurethral cylinder can be placed in 1 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 (Figures 2 and 3). Then cut 2 to 6 serial sections of each half. If 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. Even if the primary tumor is located in the glans submit the foreskin serially and in orderly fashion labeled from 1 to 12 clockwise. The rest of the penectomy specimen should be handled as described above.

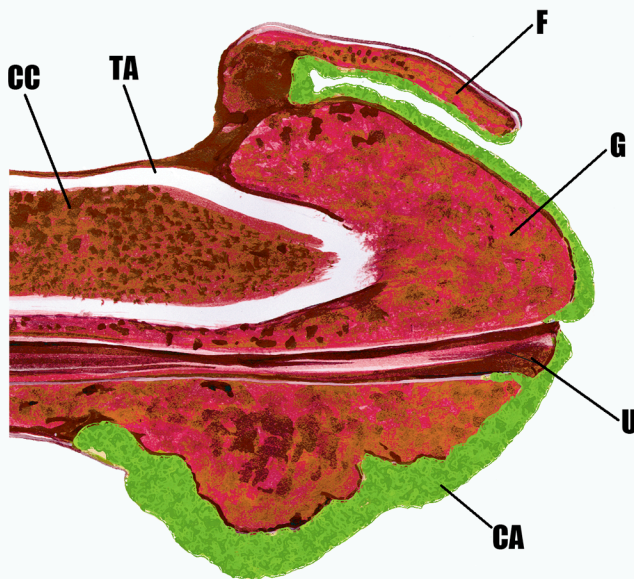


Figure 2. Partial penectomy specimen. After submitting the proximal resection margin, the specimen is cut in half longitudinally. Parallel serial sections will follow.

Abbreviations: CA, carcinoma; CC, corpus cavernosum; F, foreskin; G, glans; TA, tunica albuginea; U, urethra.

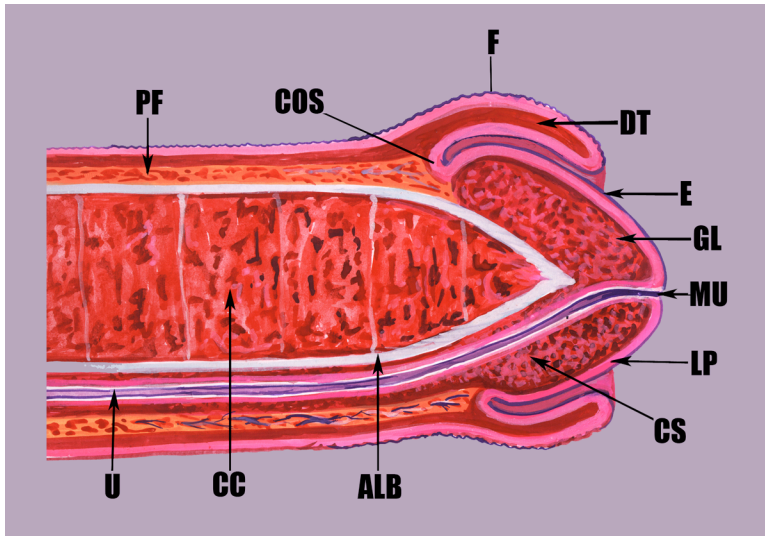


Figure 3. Longitudinal and central section showing the ventral urethra (U) and the penile main anatomic compartments: glans (GL), coronal sulcus (COS), and foreskin (F). The Buck's (penile) fascia (PF) encases the shaft and inserts into the coronal sulcus.

Abbreviations: ALB, albuginea; CC, corpus cavernosum; CS, corpus spongiosum; DT, dartos; E, epithelium; LP, lamina propria; MU, urethral meatus.

M. Pathology Report for Penile Squamous Cell Carcinoma

The report should contain the following information: Primary tumor: tumor site or sites, size in centimeters, histological subtype, histological grade, anatomical level of invasion, tumor thickness in millimeters, and vascular and perineural invasion. In penectomy specimens, the margins of resection to be reported are urethral/periurethral, corporal, and skin of the shaft.²⁸ In circumcision specimens, margins include coronal sulcus mucosal margin and cutaneous margin. Common associated lesions to be reported are penile intraepithelial neoplasia (differentiated or undifferentiated), lichen sclerosus, and other "inflammatory dermatologic" conditions.

If the specimen is accompanied by inguinal nodes, the number and size of nodes should be described. All nodes should be included for microscopic examination. The number of positive nodes and total number of nodes examined should be reported as well as the presence of extracapsular extension and the number and site (eg, inguinal versus pelvic) of metastatic nodes. The distinction between superficial and deep inguinal lymph nodes has been eliminated in the seventh edition TNM classification.¹

References

1. Edge SB, Byrd DR, Carducci MA, Compton CC, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2009.
2. 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.
3. 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.
4. 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.
5. 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.

6. Lont AP, Kroon BK, Gallee MP, van Tinteren H, Moonen LM, Horenblas S. Pelvic lymph node dissection for penile carcinoma: extent of inguinal lymph node involvement as an indicator for pelvic lymph node involvement and survival. *J Urol*. 2007;177(3):947-952.
7. Svatek RS, Munsell M, Kincaid JM, et al. Association between lymph node density and disease specific survival in patients with penile cancer. *J Urol*. In press.
8. Pandey D, Mahajan V, Kannan RR. Prognostic factors in node-positive carcinoma of the penis. *J Surg Oncol*. 2006;93(2):133-138.
9. Guimarães G, Lopes A, Campos RS, et al. Front pattern of invasion in squamous cell carcinoma of the penis: new prognostic factor for predicting risk of lymph node metastases. *Urology*. 2006;68(1):148-153.
10. Epstein JH, Humphrey PA, Cubilla AL. *Tumors of the Prostate Gland, Seminal Vesicles, Male Urethra, Penis and Scrotum*. Washington, DC: Armed Forces Institute of Pathology; In press. *Atlas of Tumor Pathology*.
11. Cubilla AL, Dillner J, Schellhammer PF, Horenblas S. Malignant epithelial tumors. In: Eble JN, Sauter G, Epstein J, Sesterhenn I, eds. *Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs*. Lyon, France: IARC Press; 2004. *World Health Organization Classification of Tumours*.
12. Velazquez EF, Barreto JE, Ayala G, Cubilla AL. Penis. In: Mills SE, Carter D, Greenson JK, et al, eds. *Sternberg's Diagnostic Surgical Pathology*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.
13. Cubilla AL, Reuter V, Velazquez E, Piris A, Saito S, Young RH. Histologic classification of penile carcinoma and its relation to outcome in 61 patients with primary resection. *Int J Surg Pathol*. 2001;9(2):111-120.
14. Cubilla AL, Velazquez EF, Reuter VE, Oliva E, Mihm MC Jr, Young RH. Warty (condylomatous) squamous cell carcinoma of the penis: a report of 11 cases and proposed classification of verruciform tumors penile tumors. *Am J Surg Pathol*. 2000;24(4):505-512.
15. 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(7):895-900.
16. Barreto JE, Velazquez EF, Ayala E, Torres J, Cubilla AL. Carcinoma cuniculatum of the penis - a distinctive variant of penile squamous cell carcinoma: report of 7 cases. *Am J Surg Pathol*. 2007;31(1):71-75.
17. Cubilla AL, Reuter VE, Gregoire L, et al. Basaloid squamous cell carcinoma: a distinctive HPV related penile neoplasm: a report of 20 cases. *Am J Surg Pathol*. 1998;22(6):751-761.
18. Velazquez EF, Melamed J, Barreto JE, Agüero F, Cubilla AL. Sarcomatoid carcinoma of the penis: a clinico-pathological study of 14 cases. *Am J Surg Pathol*. 2005;29(9):1152-1158.
19. Cubilla AL, Ayala MT, Barreto JE, Bellasai JG, Noël JC. Surface adenosquamous carcinoma of the penis: a report of three cases. *Am J Surg Pathol*. 1996;20(2):156-160.
20. Slaton JW, Morgenstern N, Levy DA, et al. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal node metastasis in penile squamous cancer. *J Urol*. 2001;165(4):1138-1142.
21. Cubilla AL, Velazquez EF, Ayala GE, Chaux A, Torres J, Reuter V. Identification of prognostic pathologic parameters in squamous cell carcinoma of the penis: significance and difficulties. *Pathol Case Rev*. 2005;10:3-13.
22. Velazquez EF, Ayala G, Liu H, et al. Histologic grade and perineural invasion are more important than tumor thickness as predictor of nodal metastasis in penile squamous cell carcinoma invading 5 to 10 mm. *Am J Surg Pathol*. 2008;32(7):974-979.
23. Chaux A, Torres J, Pfannl R, et al. Histologic grade in penile squamous cell carcinoma: visual estimation versus digital measurement of proportions of grades, adverse prognosis with any proportion of grade 3 and correlation of a Gleason-like system with nodal metastasis. *Am J Surg Pathol*. 2009;33:1042-1048.

24. Emerson RE, Ulbright TM, Eble JN, Geary WA, Eckert GJ, Cheng L. Predicting cancer progression in patients with penile squamous cell carcinoma: the importance of depth of invasion and vascular invasion. *Mod Pathol*. 2001;14(10): 963-968.
25. Guimaraes GC, Cunha IW, et al. Penile squamous cell carcinoma clinicopathological features, nodal metastasis and outcome in 333 cases. *J Urol*. 2009;182(2):528-534.
26. Leijte J, Gallee M, Antonini N, Horenblas S. Evaluation of current TNM classification of penile carcinoma. *J Urol*. 2008;180(3):933-938.
27. Chaux A, Caballero C, Soares F, et al. The prognostic index: a useful pathologic guide for prediction of nodal metastases and survival in penile squamous cell carcinoma. *Am J Surg Pathol*. 2009;33(7):1049-1057.
28. Velazquez EF, Soskin A, Bock A, Codas R, Barreto JE, Cubilla AL. Positive resection margins in partial penectomies: sites of involvement and proposal of local routes of spread of penile squamous cell carcinoma. *Am J Surg Pathol*. 2004;28(3):384-389.
29. Lopes A, Hidalgo GS, Kowalski LP, Tortoni H, Rossi BM, Fonseca FP. Prognostic factors in carcinoma of the penis: multivariate analysis of 145 patients treated with amputation and lymphadenectomy. *J Urol*. 1996;156(5):1637-1642.
30. Ficarra V, Zattoni F, Cunisco SC, et al. Lymphatic and vascular embolizations are independent predictive variables of inguinal node involvement in patients with squamous cell carcinoma of the penis: Gruppo Uro-Oncologico del Nord Est (Northeast Uro-Oncological Group) Penile Cancer data base data. *Cancer*. 2005;103(12):2507-2516.
31. Ficarra V, Zattoni F, Artibani W, et al; GUONE Penile Cancer Project Members. Nomogram predictive of pathological inguinal lymph node involvement in patients with squamous cell carcinoma of the penis. *J Urol*. 2006;175(6):1700-1705.
32. Kattan MW, Ficarra V, Artibani W, et al; GUONE Penile Cancer Project Members. Nomogram predictive of cancer specific survival in patients undergoing partial or total amputation for squamous cell carcinoma of the penis. *J Urol*. 2006;175(6):2103-2108.
33. Novara G, Galfano A, De Marco V, Artibani W, Ficarra V. Prognostic factors in squamous cell carcinoma of the penis. *Nat Clin Pract Urol*. 2007;4(3):140-146.
34. Solsona E, Algaba F, Horenblas S, Pizzocaro G, Windahl T; European Association of Urology. EAU guidelines on penile cancer. *Eur Urol*. 2004;46(1):1-8.
35. Solsona E, Iborra I, Rubio J, Casanova JL, Ricos JV, Calabuig C. Prospective validation of the association of local tumor stage and grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. *J Urol*. 2001;165(5):1506-1509.
36. Hungerhuber E, Schlenker B, et al. Risk stratification in penile carcinoma: 25-year experience with surgical inguinal lymph node staging. *Urology*. 2006;68(3):621-625.
37. Ornellas AA, Nóbrega BL, Wei Kin Chin E, et al. Prognostic factors in invasive squamous cell carcinoma of the penis: analysis of 196 patients treated at the Brazilian National Cancer Institute. *J Urol*. 2008;180(4):1354-1359.
38. Cubilla AL, Pfannl R, Rodriguez I, et al. Morphological characterization and distribution of penile precancerous lesions using a simplified nomenclature: a study of 198 lesions in 115 patients. *Lab Invest*. 2008;88:696(A).
39. Pfannl R, Hernandez M, Velazquez EF, et al. Expression of p53 and p16 in differentiated and warty/basaloid penile intraepithelial neoplasia (PeIN). *Lab Invest*. 2008;88:807(A).
40. Cubilla AL, Piris A, Pfannl R, Rodriguez I, Agüero F, Young RH. Anatomic levels: important landmarks in penectomy specimens; a detailed anatomic and histologic study based on the examination of 44 specimens. *Am J Surg Pathol*. 2001;25:1091-1094.