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

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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
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

+ 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.
+ 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

Macrosopic 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 connetive 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

+ 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.
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 connetive 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. Phimosis is present in up to one-half of patients with penile carcinoma, and its presence is considered a risk factor for the development of this tumor.

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. 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.

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.

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. There are other SCC variants showing distinctive morphological and outcome features. 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. More recently described subtypes, such as pseudohyperplastic and carcinoma cuniculatum of the penis, also belong to this category of excellent prognosis. The high-risk category is comprised by basaloid, sarcomatoid, adenosquamous, and poorly differentiated SCC of the usual type. 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.

E. Histological Grade
Histological grade has been consistently reported as an influential predictive factor of groin metastasis and dissemination of penile cancer. 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.
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 dartos\(^{28}\) (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](image-url)
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. The new TNM staging classification in the seventh edition of the AJCC Cancer Staging Manual 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. 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. 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. 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. 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.

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. 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 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.

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

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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).\textsuperscript{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).\textsuperscript{40} If present, classify the foreskin as short, medium, long, and/or phimotic.\textsuperscript{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 multiples 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. 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.

References


