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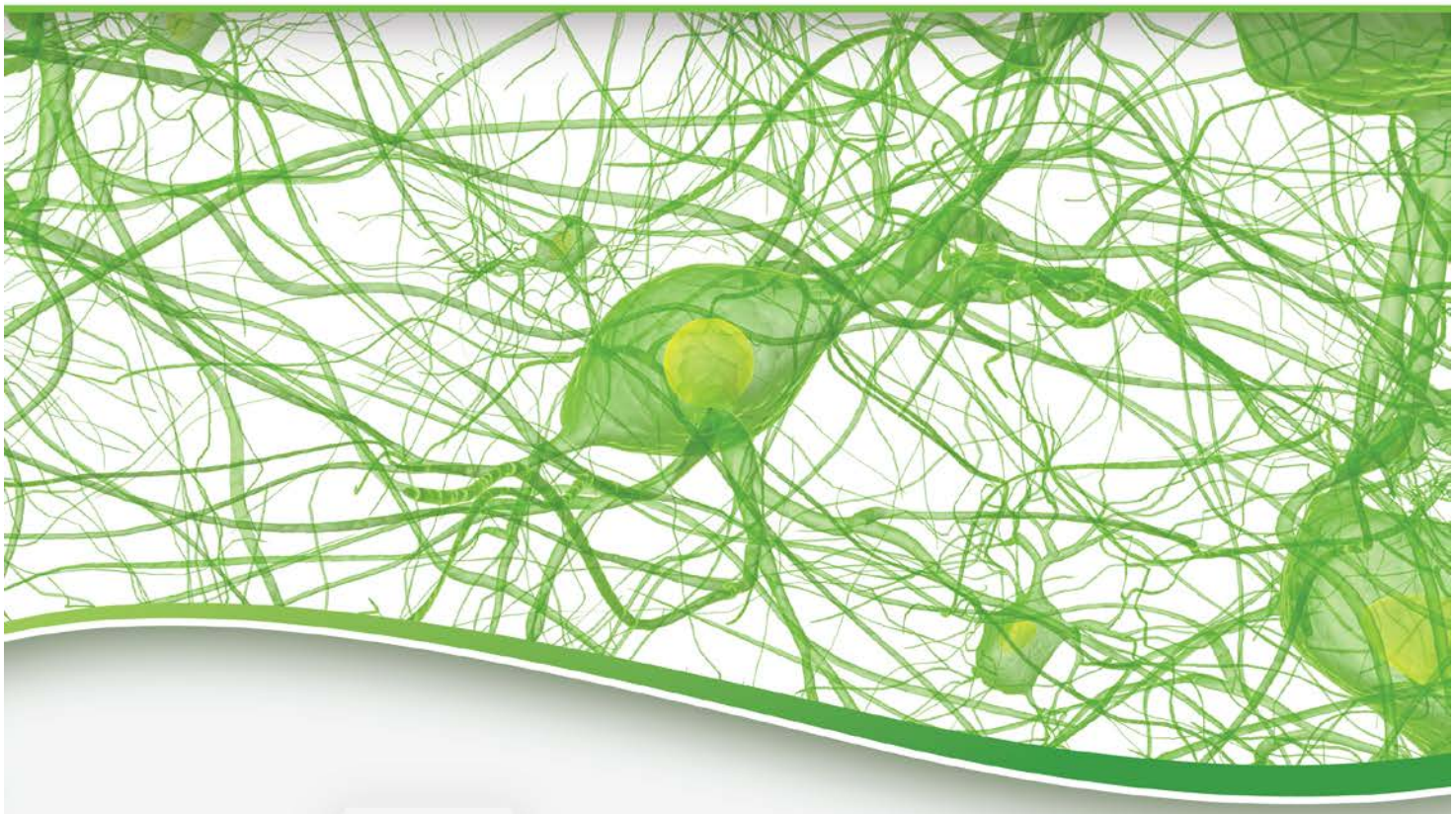

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Update On TNM Staging of Penile Cancer

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As with malignant tumors of all organs, the AJCC TNM staging system provides a helpful tool for the urologist and oncologists to plan management strategies and provides prognostic information to the patient. The importance of accurate staging of the primary tumor is critical for patient management, and therefore is essential for the pathologist to understand and strictly apply these criteria. It should be noted that TNM staging of the penis is only applicable to squamous cell carcinomas, and does not apply to melanomas, sarcomas or urethral carcinomas.

Pathologic TNM Staging of Penile Tumors Prior to the 8th Edition

Considering the low incidence of penile cancer in the United States of America, TNM staging of penile carcinomas was not developed until the 3rd edition of the TNM Cancer Staging Manual in 1988. The 3rd edition TNM staging system did not undergo any changes till the 7th edition, which was published in 2010. In the 7th edition, pT1 stage was subdivided into pT1a and pT1b, depending on the presence or absence of lymphovascular invasion, and/or the presence or absence of a poorly differentiated carcinoma component. Lymph node involvement was also updated in the 7th edition, with pN1 and pN2 categories changed to inguinal lymph node (to include both superficial and deep lymph nodes) involvement, rather than just superficial inguinal lymph node involvement used in the 3rd through 6th editions. The pN3 category, in the 7th edition, was changed to include extra-nodal extension of squamous cell carcinoma in the lymph node.

Updates Between 7th Edition and 8th Editions:

The 8th edition has important differences, compared to the prior editions of the TNM stage designations. For the first time, the pT1 category is also dependent on the location of the tumor on the penis (further discussed below). One of the most significant changes between the 7th and 8th editions has been the designation of stage pT3 to invasion of the corpora cavernosa; compared to the prior pT2 stage designation that included both corpus spongiosum and corpora cavernosa invasion. Other significant changes include those of pTa, pT1, pN1 and pN2 stages. Each pT and pN stage is listed below along with practical information to help the practicing pathologist assign a pathologic stage for primary penile squamous cell carcinoma.

pTX: The primary tumor cannot be assessed, which is a rare occurrence in penile squamous cell carcinoma.

pT0: There is no evidence of tumor. This usually occurs when small tumors are biopsied and there is no residual tumor identified in the subsequent resection.

pTis: Carcinoma in-situ, which is now referred to as Penile Intraepithelial Neoplasia (PeIN).

pTa: The tumor is localized and non-invasive. In this designation the term "non-invasive verrucous carcinoma", which has persisted from the 3rd to the 7th edition, has been changed to the aforementioned. pTa now includes verrucous carcinoma, and, other non-invasive squamous cell carcinomas, which are not the same as carcinoma in-situ. The tumor and surrounding penile tissue need to be extensively sampled to assign this stage. The term "non-invasive verrucous carcinoma" was changed since pathologists and clinicians assumed all verrucous carcinomas were non-invasive. Verrucous carcinomas have a smooth pushing invasive front, but occasionally have overt destructive invasion that is staged as pT1. The other non-invasive squamous cell carcinomas differ from carcinoma in-situ in that they project above the penile surface, unlike carcinoma in-situ, which is a flat lesion. This designation for non-invasive squamous cell carcinomas is similar to the difference between urothelial carcinoma in-situ (a flat lesion) and non-invasive papillary urothelial carcinoma of the urinary bladder.

pT1: Tumor is invasive into the lamina propria. pT1 was first divided into pT1a and pT1b in the 7th edition, based on the presence or absence of lymphovascular invasion and/or poorly differentiated carcinoma component. Stage pT1a is lamina propria invasion without the lymphovascular invasion or poorly differentiated carcinoma component; while pT1b includes those pathologic criteria. In the 8th edition, presence or absence of perineural invasion has been added to lymphovascular invasion and poorly differentiated carcinoma component. In addition, for the first time, the layers of tissue invaded by the tumor are defined by the location of the tumor on the penis. Pathologic stage pT1 is the only one that can be assigned to invasive tumors in the foreskin, as none of the structures included in pathologic stage pT2 (corpus spongiosum) or pT3 (corpus cavernosum) are present in the foreskin. pT1 invasion in the foreskin may extend from the skin surface invading down toward the squamous mucosa; or, it may extend outward from the squamous mucosa towards the skin. Tumors arising on the glans penis are invasive into the underlying lamina propria for a pT1 designation. On the penile shaft, pathologic stage pT1 includes invasion anywhere between the epidermis of the penile skin and the underlying tunica albuginea and/or corpus spongiosum. On the penile shaft pathologic stage pT1 includes invasion into the dermis and Buck's fascia.

pT2: Tumor invasive into corpus spongiosum, with or without urethral invasion. An important shift in the pT2 category has been deletion of corpus cavernosum invasion from this designation, which was present in the TNM staging from the 3rd to the 7th editions. In the 8th edition, pT2 only includes corpus spongiosum invasion. Corpus cavernosum invasion was excluded from the pT2 designation as the corpora cavernosa are surrounded by the tunica albuginea (see pT3 section), whereas the corpus spongiosum does not have this barrier to stop the spread of tumor. pT2 applies to tumors arising in the glans penis, coronal sulcus and the penile shaft, but not to tumors of the foreskin, since there is no corpus spongiosum in the foreskin. Most pT2 tumors involve the glans penis, followed by the coronal sulcus. pT2 tumors of the penile shaft

are uncommon, and tend to arise on the ventral aspect where the corpus spongiosum is closest to the skin surface.

pT3: Tumor invasive into corpus cavernosum, including tunica albuginea, with or without urethral invasion. As mentioned above, corpus cavernosum invasion is now designated as pT3 in the 8th edition. The corpora cavernosa are completely surrounded by the tunica albuginea, which is a dense fibroelastic tissue. Considering its thickness and dense nature, tunica albuginea acts as a natural barrier to the spread of tumor into the corpus cavernosum. Invasion into the tunica albuginea is also considered pT3 disease.

pT4: Tumor invades adjacent structures such as the scrotum, pubic bone or prostate gland. These are rare occurrences, except in patients who avoid seeking medical care.

pNx: Lymph node metastasis cannot be established.

pN0: No lymph node metastasis.

pN1: Metastasis in one or two inguinal lymph nodes from the same side, but without extra-nodal extension. In the 8th edition the number of positive lymph nodes was changed, from a single positive inguinal lymph node in the 7th edition, to one or two positive lymph nodes, but without extra-nodal extension.

pN2: Metastasis in three or more inguinal lymph nodes from the same side without extra-nodal extension, or, any number of positive inguinal lymph nodes on both sides without extra-nodal extension. As mentioned above in the pN1 section, the number of positive lymph nodes has changed. In prior editions the word “multiple” lymph nodes was used; however, the 8th edition was updated to include a specific number of three or more positive lymph nodes. As with pN1 there should be no extra-nodal extension in the positive lymph nodes.

pN3: Metastasis to any number of inguinal lymph nodes with extra-nodal extension, or, metastasis to pelvic lymph nodes. There is a minor change in verbiage for this category between the 7th and 8th editions. The word “inguinal” was added in the 8th edition to lymph nodes with extra-nodal extension. Also, the words “unilateral or bilateral” were removed for the pelvic lymph node involvement.

M stage: There has been no change in the M stage since the 3rd edition.
AJCC Prognostic Stage Groups:

The **Stage Groups** for the updated 8th edition are listed below. The only update from the 7th edition has been the division of Stage II, into Stage IIA and Stage IIB.
Stage 0is: pTis, pN0, M0
Stage 0a: pTa, pN0, M0
Stage I: pT1a, pN0, M0

Stage IIA: pT1a, pN0, M0; or, pT2, pN0, M0
Stage IIB: pT3, pN0, M0
Stage IIIA: pT1-pT3, pN1, M0
Stage IIIB: pT1-pT3, pN2, M0
Stage IV: pT4, Any N, M0; or, Any pT, N3, M0; or, Any pT, Any N, M1

Importance of Anatomy of the Penis in TNM stage:

Clarity in understanding the anatomy of the penis is crucial to providing an accurate pT stage. In anatomical terms, the penis does not have a superior and inferior aspect, but rather dorsal and ventral aspects. From the anatomic point of view the penis is described as it appears in the erect position, therefore the dorsal aspect faces the abdomen, while the ventral aspect faces outwards. The penis has different anatomic structures based on the four areas the penis is divided into, i.e., penile root, penile shaft glans penis and foreskin. Excellent illustrations of penile anatomy are available in the 4th series Fascicle on tumors of prostate, seminal vesicle and penis from the American Registry of Pathology.

The most proximal part is the root of the penis, which is composed of the two cylindrical corpora cavernosa (corpus cavernosum is the singular) that are separated within the root and are attached to the anterior aspect of the ipsilateral ischium bone. Highly aggressive tumors of the penile shaft may extend to the penile root.

Distal to the root is the penile shaft, which ends just at the coronal sulcus of the glans penis. The two cylindrical corpora cavernosa run along the dorsal aspect of the shaft and come to a point in the glans penis. There is a variable length of corpora cavernosa in the glans penis. The corpora cavernosa are ensheathed in a dense fibroelastic tissue called the tunica albuginea, which also serves as a barrier to spread of tumor into the corpora cavernosa. The dorsal penile vein runs along the groove between the two corpora cavernosa on the dorsal aspect, while the corpus spongiosum surrounding the urethra runs along the ventral aspect. Both the corpus spongiosum and the tunica albuginea (with the ensheathed corpora cavernosa) are surrounded by a loose fibrovascular connective tissue known as Buck's fascia. The skin forms the outermost layer. Tumors arising on the penile shaft are less common than those involving the glans penis. Tumors arising from the dorsal aspect of the penile shaft first invade into the dermis followed by Buck's fascia (pT1), followed by tunica albuginea and corpora cavernosa (pT3); corpus spongiosum invasion is less common except in highly aggressive tumors. Tumors arising from the ventral aspect of the shaft are less common than those from the dorsal shaft, but these tend to invade into the corpus spongiosum more often.

The glans penis is formed as a conical expansion of the distal end of the corpus spongiosum. The urethra, which is surrounded by the corpus spongiosum, is located on the ventral aspect of this cone. The surface of the glans penis is covered by squamous mucosa, which is reflected on to the inner aspect of the foreskin at the coronal sulcus. The squamous mucosa may be keratinized, especially in circumcised patients. It is important to note that the glans penis is covered by squamous mucosa and not by skin.

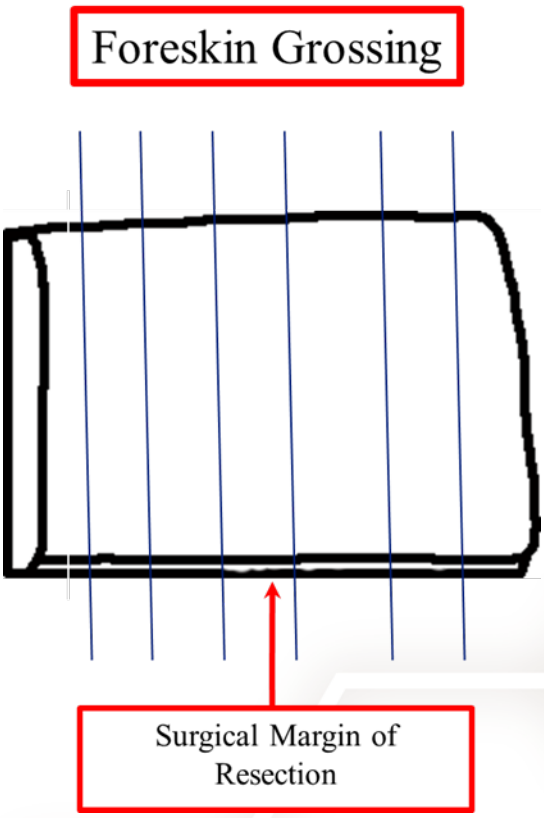
This is important in cases where inadequate clinical information about the location of the biopsy is provided by the urologist. If there is tumor surrounded by skin it is not likely a tumor arising from the glans penis. There is a variable amount of lamina propria between the corpus spongiosum and the overlying squamous mucosa. The lamina propria and corpus spongiosum sometimes blend into each other, as there is no distinct barrier between these two structures; which may sometimes make it difficult to decide on pT1 (lamina propria invasion) versus pT2 (corpus spongiosum invasion). A variable amount of corpus cavernosum is present in the glans; as in the shaft, the corpora cavernosa are surrounded by the tunica albuginea that comes to a point in the glans penis.

The foreskin is the distal most end of the penile skin, and is composed of multiple layers. The outermost is a continuation of the penile skin, with underlying dermis, lamina propria, dartos muscle and the innermost squamous mucosa, which as mentioned above is a reflection of the squamous mucosa of the glans penis at the coronal sulcus.

Gross examination of the Penis for optimal staging:

As with all organs understanding the anatomy and using the correct grossing technique is essential for providing the correct pathologic T stage. To comprehend staging of penile tumors one needs to understand the anatomy, especially since it varies between the three main components of the penis; i.e., foreskin, glans penis and penile shaft. Pathologists also need to be aware of the different types of surgical specimens they may receive from the urologist, operating on a patient with penile cancer, in order to better understand how to gross them. There are excellent sketches of these specimens and grossing techniques available in the Royal College of Pathologists dataset for penile and distal urethral tumors (https://www.rcpath.org/resourceLibrary/dataset-for-penile-and-distal-urethral-cancer-histopathology-reports.html); and, in the 4th series Fascicle on tumors of prostate, seminal vesicle and penis from the American Registry of Pathology. These are in sharp contrast to the rudimentary line drawings provided here solely for illustration purposes.

Circumcisions for tumors of the foreskin are generally the easiest specimen to orient and gross. The specimen is a rectangular piece of skin and squamous mucosa. There is only one surgical margin in the circumcision specimen, which is along the long axis of the specimen, where the skin and mucosa are incised at the coronal sulcus. Opposite to the surgical margin is where the skin folds over to the squamous mucosa surface of the foreskin, and this is not considered a margin. The cut surface along the short axis is not a margin either, since this incision is to remove the foreskin after it is excised off the coronal sulcus and skin of the penile shaft. After inking the margin, the specimen should be stretched out and fixed in formalin overnight to ensure adequate fixation, as to provide good sections for histology. The specimen should be sliced perpendicular to the long axis of the surgical margin, so each section demonstrates the skin, lamina propria, dartos muscle and the squamous mucosa. Most invasive foreskin

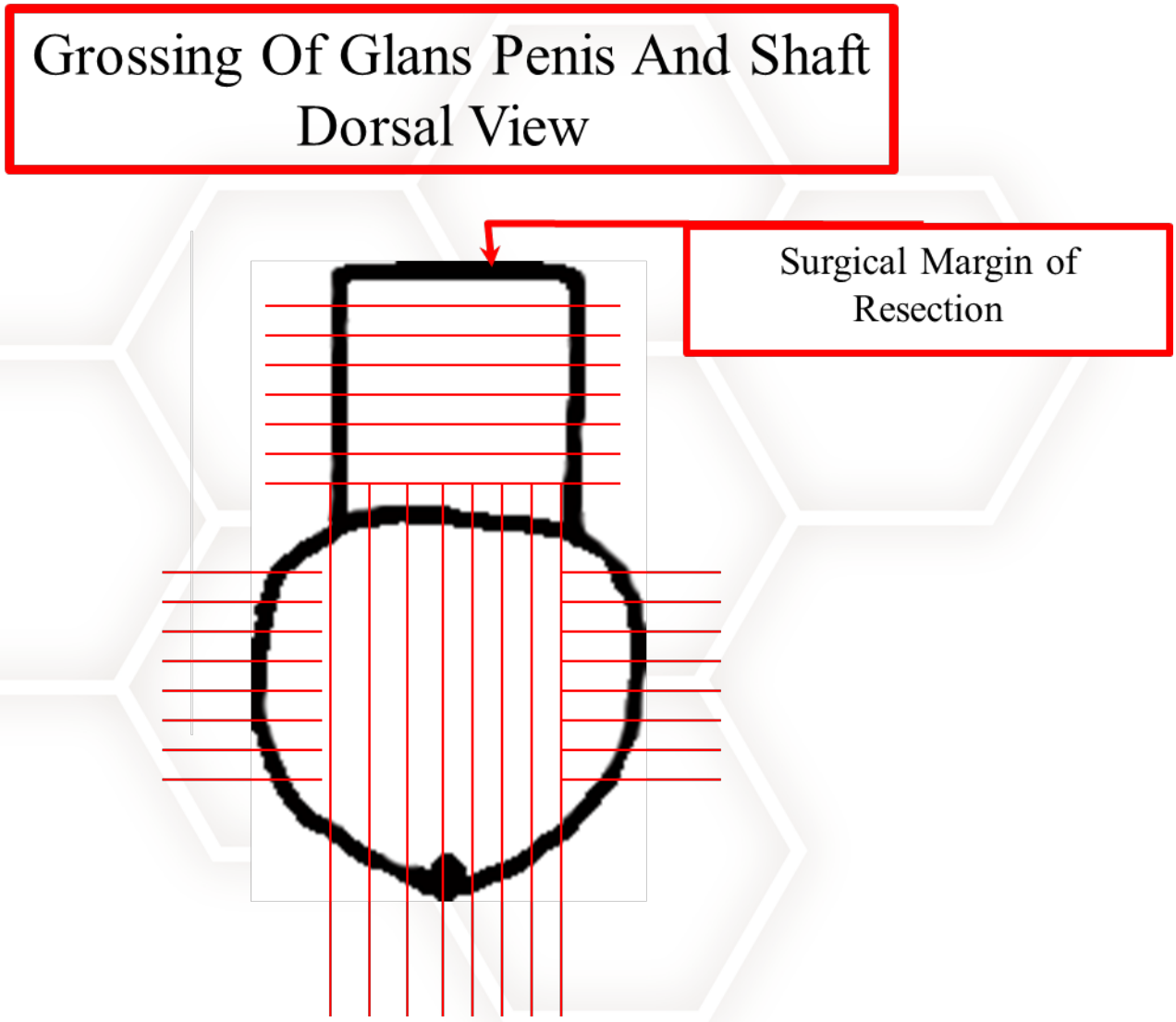


tumors are pT1; unless they extend along the surface of the glans penis and invade into the corpus spongiosum of the glans penis.

Functional preservation is generally the goal for resections of glans penis tumors; therefore, the resection types can vary depending on the size of the tumor. For small tumors, that appear minimally invasive the surgeon may elect for a local excision where only a small part of the glans penis with the underlying corpus spongiosum is resected. Depending on the urologist these may be sent for frozen section evaluation of the margin. It is easiest to ink the resected margins and submit the entire specimen for frozen section to evaluate the depth of tumor invasion and all the margins. The glans sparing partial penectomy is an extension of the local excision for small tumors; where a larger surface of the glans along with some (not all) of the superficial corpus spongiosum is excised. Depending on the tumor location the coronal sulcus and/or a short segment of the urethra may also be excised. If intra-operative margin evaluation is requested, it is best to ink the margin and submit the entire specimen for frozen section evaluation. If the specimen is oriented by the surgeon as to distal and proximal, it should be sectioned perpendicular to the proximal margin, so the tumor and all margins can be evaluated, especially the deep margin. In specimens like these with a short segment of urethra, the proximal urethral margin should be inked and submitted en face before the other margins are inked. The partial penectomy without corpus cavernosum excision involves excising the glans penis without opening the tunica albuginea or excising the corpora cavernosa. This specimen includes the glans penis with a segment of urethra, and/or penile skin if the patient is not circumcised. If intra-operative margin evaluation is requested, the glans penis margin and the urethral margin need to be inked. The right and left sides can be inked different colors. All these margins are submitted en face for frozen section evaluation. It is important to note that as the urethra, corpus spongiosum and skin freeze at different rates, it is best to freeze them in separate blocks. The usual partial penectomy specimen includes the entire glans penis and a short segment of the penile shaft, including the skin. As with the other type of partial penectomy, all margins are inked, embedded en face and submitted separately if frozen section evaluation of margins is requested.

The total penectomy includes the entire penile shaft and the glans penis. The length of urethra resected is variable, depending on the length required for implantation in the perineum. Frozen section evaluation of margins in these specimens is usually limited to the proximal end of the corpora cavernosa and the urethra. Sometimes the skin margins are also evaluated.

All penectomy specimens, except for small specimens submitted entirely for frozen section evaluation, need to be fixed overnight as the different layers fix at different rates. The glans penis is grossed the same in partial penectomies and total penectomies. The glans penis is cut into a right and left half by slicing through the sagittal plane dividing the urethra and glans penis into two halves. Subsequent sections are taken parallel to the first cut (parasagittal sections). The lateral most ends of both sides are sliced as coronal sections. This method of grossing easily allows the evaluation of the tumor and its maximum depth of invasion. The sections submitted should allow for evaluation of the entire tumor, unless it is quite large. For total



penectomies the penile shaft is amputated a few centimeters proximal to the glans penis, which is grossed in a similar fashion as above. The penile shaft is serially cross-

sectioned from distal to proximal, so each cross section shows all the structures of the shaft (skin, Buck's fascia, corpus spongiosum and corpora cavernosa).

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