

Review

Handling and Pathology Reporting of Circumcision and Penectomy Specimens[☆]

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1. Introduction

Cancer of the penis is an extremely rare neoplasm in Western countries where the relative frequency of the tumor is below 1%. In Africa, Asia and some countries in South America penile cancer accounts for up to 20% of all malignancies in men [1]. The most important etiologic factors seem to be the “uncircumcised foreskin” [2]. Some 25% of patients with penile cancer have a history of phimosis [3]. Jewish men have the lowest incidences because they are circumcised earlier in life than Muslims, who have higher incidences [2]. There is also a strong association with HPV infection (types 16 and 18) which can be detected in 40–50% of penis cancer patients [4]. Other risk factors are smoking, sexual behaviour and ultraviolet A photochemotherapy (PUVA) in psoriatic patients.

2. Clinical presentation and surgical procedures

The clinical presentation of penis cancer may range from small erythematous lesion to ulcer or verrucous

exophytic growing tumors. As a rule all lesions of foreskin and glans (Table 1) which do not resolve after local therapy should be excised and submitted for histology [2]. The clinical evaluation includes also the inspection of the inguinal lymph nodes which are enlarged in more than 1/2 of the patients [5] but most have a reactive lymphadenopathy. However, about 45% of palpable and 20% of nonpalpable inguinal lymph nodes contain metastases [6].

Small lesions of the foreskin can be treated by circumcision; the recurrence rate is however rather high [7]. Carcinoma involving the glans and the shaft are best managed by partial penectomy, bulky tumors require a total penectomy with perineal urethrotomy, with or without local lymphadenectomy [8]. Another approach is the use of sentinel node for the staging of penis cancer [9].

The aim of these guidelines is to establish the criteria for the processing, histological diagnosis and reporting of penis cancer and its forerunners (Table 2).

3. Handling of the surgical specimen [10,11]

Before starting with the gross description and dissection, the anatomy of the organ should be called to mind. The penis is composed of the glans, balanopreputial (coronal) sulcus and the prepuce (foreskin). The central portion is formed by the shaft and the posterior end is the root of the penis. More important for the

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Table 1

Frequent localization of penile cancer [2]

Glans	48%
Prepuce	21%
Glans + prepuce	9%
Shaft	2%

tumor staging are the structures seen on the cross-section. From outer to inner, the cross-section shows the following structures: skin and the attached muscle, fascia penis superficialis and profunda (Buck's fascia), tunica albuginea, corpora cavernosa and the urethra which is surrounded by the corpus spongiosum with its own tunica albuginea. The two A. superficiales penis and the veins are located between the fascia penis superficialis and the tunica albuginea. The two A. profundae penis are in the middle of the right and left corpus cavernosum. The lymphatic channels drain to the deep and superficial inguinal lymph nodes.

3.1. Circumcision

The epithelial margins of the specimen have to be inked. The four corners of the foreskin should be pinned on a tablet (or even better on a sheet of cork) and then the whole specimen fixed in formalin. After fixation the number and size of lesions are recorded and their gross pathology described. For histology serial perpendicular sections are performed—the number of sections depends on the dimension of the lesion. Obviously, each epithelial margin should be sampled.

3.2. Total or partial penectomy

Before beginning dissection the anatomical location of any lesion should be identified and its size measured. Then a shave section of the shaft (surgical margin) is taken. The specimen is mostly large and must be divided in two parts. Especially in frozen sections

Table 2

Clinical information

Patient identification	
Identification number	
Name	
Birth date	
Clinical information	
Relevant history (HPV infection, PUVA treatment, smoking, sexual behaviour)	
Anatomic site	
Operative findings	
Procedure	
Circumcision	
Excision	
Total/partial penectomy	
Lymphadenectomy	
Responsible physician(s)	

Table 3

Macroscopic examination

Specimen unfixated/fixated	
Structures included in specimen	
Foreskin	
Glans	
Penis shaft	
Urethra	
Urethra opened/unopened	
Size of the surgical specimen	
Results of intraoperative consultation	
Tumor (if identified)	
Location	
Size	
Descriptive features	
Extent	
Regional lymph nodes/sentinel lymph node	
Location	
Number	
Blocks submitted for microscopic evaluation	
Tumor(s) ^a	
Shaft margin including skin, erectile bodies and urethra	
Foreskin	
Transverse section of the shaft	
Longitudinal section through the glans including a section with the urethra	
Frozen section tissue	
Special studies (specify) (e.g. immunohistochemistry, DNA ploidy analysis)	

^a Submit tumor sections that show the relationships to the adjacent surface epithelium, urethra, and erectile bodies.

the urethra and the periurethral corpus spongiosum should be separately examined because this is the region of invasive tumor spread [11]. After the foreskin has been removed and if necessary pinned on a table or cork, the penis should be longitudinally bisected using the urethra as a guide. Parallel sections of the glans can be additionally performed. The size and depth of any tumor should be documented. For histology sections of the tumor, foreskin, transverse section through the shaft and longitudinal glans sections are required and the resection margin as described above (Table 3).

3.3. Lymphadenectomy and/or sentinel lymph node

Lymph nodes without overt metastasis greater than 5 mm are cut through the hilus in 2 mm thick parallel slices. Lymph nodes smaller than 5 mm along the longitudinal axis are entirely processed. When the lymph node contains an evident metastasis 1–2 sections are usually enough.

Sentinel lymph nodes are often detected with lymphoscintigraphy [2,7] and are labeled with radioactive colloid. Negative lymph nodes are entirely processed (steps of 250 µm). Every second section could be used for cytokeratin immunocytochemistry (Tables 3 and 4).

Table 4

Microscopic evaluation

Tumor
Location(s)
Histological type
Malignancy grade
Depth of invasion (mm or μm)
Vascular invasion
Margin
Regional lymph nodes
Number (specify location if possible)
Number involved by tumor
Specify location
Size of metastatic deposit
Extracapsular extension, if present
Additional pathological findings if present
Intraepithelial neoplasia (Mb. Bowen, Erythroplasia of Queyrat)
Therapy related changes
Other(s)
Metastasis in other organs
Other tissue(s)/organs
Results of special studies
Comments
Correlation with intraoperative consultation
Correlation with other specimens
Correlation with clinical information

3.4. Frozen section

Frozen sections can be used for the evaluation of the resection margins and of the sentinel lymph node.

3.4.1. Resection margins

Usually the tumor spreads in the urethra and periurethral vessels and soft tissue, which should thus be frozen for histological evaluation. In circumcision specimens the entire circumference and thickness of the surgical margin should be frozen and evaluated [9]. To avoid unnecessary sections the surgeon can mark the area of concern with a suture.

3.4.2. (Sentinel) lymph nodes

When a frozen section is requested the lymph node should be bisected and one section (not more!) from each cut surface should be made. Then both halves are embedded and the first slides H&E stained.

4. Pathology reporting of surgical specimens (circumcision and penectomy)

The pathology report should provide useful information for the therapy and prognosis of the penile lesions. It should thus include the histological diagnosis and all other factors which have a predictive value (Table 4).

Table 5Histological classification of premalignant lesions and most frequent tumors of the penis^a

Epithelial lesions
Premalignant
Carcinoma in situ (erythroplasia of Queyrat and Bowen's disease)
Other
Bowenoid papulosis
Malignant
Squamous carcinoma
Usual type (NOS)
Papillary carcinoma (NOS)
Verrucous carcinoma
Warty (condylomatous) carcinoma
Basaloid carcinoma
Sarcomatoid carcinoma
Adenosquamous carcinoma
Mixed carcinomas
Basal cell carcinomas
Paget's disease
Other rare carcinomas [23]
Melanocytic
Nevi
Malignant melanoma
Mesenchymal tumors

^a Modified after Cubilla [9].

For the penis tumors in general only the histological type, the depth of invasion (stage) and the tumor grade are of prognostic significance.

4.1. Histology of the precursor lesions

The only precursor lesion is the squamous carcinoma in situ of the penis, which may be referred to as Bowen's disease or erythroplasia of Queyrat. Both are identical in clinical course and histological features but may vary in their clinical presentation. 5–10% of these lesions progress to carcinoma [9].

Bowenoid papulosis is now considered to be a sexually transmitted disease, probably caused by human papillomavirus type 16, which affects young men. In spite of histological similarity to the carcinoma in situ the lesion usually regresses spontaneously, but cases with malignant transformation have been documented [12].

4.2. Histology of penis cancer

More than 95% of malignant penis tumors are more or less differentiated squamous carcinomas [9]. However, there are several subtypes with their own epidemiology and biology (Table 2). The most frequent are those of the so-called "verruciform group" [9,11,13,14]. The histological appearance is of prognostic importance (Table 5).

Table 6

Standard histological grading

Grade 1	Well differentiated cells with typical intracellular bridges and marked keratinization with the production of typical keratin pearls. The degree of anaplasia and the number of mitotic figures are low.
Grade 2	Single cell keratinization, no keratin pearls and a higher number of mitoses and anaplastic cells.
Grade 3	Poor cell differentiation with numerous mitoses and complete lack of keratinisation.
Grade 4	Undifferentiated carcinomas ^a

^a Although in this location extremely rare tumors the category should be used for all carcinomas which a priori do not show any differentiation (e.g. small cell anaplastic neuroendocrine carcinomas).

The usual type *squamous carcinoma (NOS)* is a superficial spreading, commonly slowly growing carcinoma with keratin production. Frequently the tumors are well or moderately differentiated. The association with HPV infection can be encountered in 25–45% of cases and is lower than in the group of warty neoplasm [11,13,14]. The prognosis depends on the grade of malignancy and TNM tumor stage.

The most common penis tumor with exophytic growth is the *papillary carcinoma NOS* which seems to be closely related to the usual type of penis carcinoma. The tumors can be well or moderately differentiated (G1–2) and can metastasize. Koilocytic atypia are not present [9,11].

The *verrucous carcinoma* is an exophytic growing well differentiated neoplasm which can be confused with a benign lesion. The atypia is minimal (always grade 1) and HPV related koilocytic cells are absent. The base of the tumor shows pushing borders and no true invasion. As in usual squamous carcinoma only about 1/3 of the cases are positive for HPV DNA [14]. The prognosis is excellent.

Warty (condylomatous) carcinomas are 100% positive for HPV DNA [14]. The hallmarks of the tumor are the koilocytic atypia and abundant mitoses [9]. They are slowly growing tumors, which however can metastasize.

The *basaloid carcinoma* is a very aggressive invasive growing cancer with poor prognosis. The tumor is composed of poorly differentiated basophilic cells and shows comedo necrosis. Keratinization can be present. The tumor is frequently (86%) HPV positive [14].

Sarcomatoid carcinomas are poorly differentiated tumors made of spindle cells resembling fibro- or leiomyo-sarcomas. The use of cytokeratin antibodies is helpful for the correct diagnosis.

Some tumors show a mixed histological pattern and are also called *hybrid carcinomas* [9]. Rare carcinoma types are: adenosquamous carcinoma, adenocarcinoma, neuroendocrine, basal cell and sebaceous carcinoma.

Melanomas, sarcomas of different types and the Paget disease of the penis are exceptionally rare

tumors. The surgical treatment and the pathological processing of the material do not differ from those of carcinomas. The outcome is tumor specific but the prognosis is mostly poor.

4.3. Grading of squamous carcinomas

The “classical” grading is based on the degree of cell anaplasia (Table 6). The well differentiated (G1) squamous carcinoma still retains the capability of keratinization with the production of typical keratin pearls. The typical intracellular bridges are clearly seen and the degree of anaplasia as well as the number of mitotic figures are low. The moderately differentiated (G2) squamous carcinoma does not show keratin pearls but only single cell keratinization and a higher number of mitoses and anaplastic cells. Mitoses, poor complete

Table 7

An optional scoring system for squamous carcinoma [16]

Degree of keratinization
Points
0: No keratin pearls. Keratin in <25 percent of cells
1: No keratin pearls. Keratin in 25 to 50 percent of cells
2: Keratin pearls incomplete or keratin in 50 to 75 percent of cells
3: Keratin pearls complete or keratin in >75 percent of cells
Mitotic activity
Points
0: 10 or more mitotic cells/field
1: 6–9 mitotic cells/field
2: 3–5 mitotic cells/field
3: 0–2 mitotic cells/field
Cellular atypia
Points
0: All cells atypical
1: Many atypical cells/field
2: Moderate number of atypical cells/field
3: Few atypical cells/field
Inflammatory cells
Points
0: No inflammatory cells present
1: Inflammatory cells (lymphocytes) present
Grade 1: 8–10 points
Grade 2: 5–7 points
Grade 3: 3–4 points
Grade 4: 0–2 points

Table 8

Staging—TNM Classification 2002 [18]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Noninvasive verrucous carcinoma
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra or prostate
T4	Tumor invades other adjacent structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single superficial inguinal lymph node
N2	Metastasis in multiple or bilateral superficial inguinal lymph nodes
N3	Metastasis in deep inguinal or pelvic lymph node(s), unilateral or bilateral
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

cell differentiation and the lack of keratinization are the morphological hallmarks of the poorly differentiated (G3) penis carcinomas. The presence of more than 50% of poorly differentiated cancer is a strong predictor of lymph node metastases [15].

A more sophisticated grading (Table 7) based on the degree of keratinization, cell atypia, mitotic activity and amount of the inflammatory cell infiltrate has been proposed by Maiche et al. [16]. Cubilla [9] combines the classical grading with the anatomical level of invasion in attempt to predict lymph node metastases.

The histological grading is also important for the surgical management of the penis carcinoma. Grade 1–2 cancers require a 10 mm and G3 a 15 mm margin of clearance [17].

4.4. Staging

For tumor staging the TNM system is now accepted worldwide (Table 8). The T stage is based on the vertical invasion of the different anatomical structures (subepithelial connective tissue, corpus spongiosum or cavernosum, urethra, prostate, adjacent structures).

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Table 9

Morphological factors predicting lymph node or systemic metastases

Aggressiveness according to anatomical location: coronal sulcus > glans tumors > foreskin
Vertical invasive growth
Depth of invasion >9 mm
Vascular invasion
Sarcomatoid or basaloid carcinomas
Amount of poorly differentiated tumor >50%
p53 positivity

The suggestion of Cubilla [9] to subcategorize T2 in T2a for the invasion of corpus spongiosum only and T2b for the invasion of the corpus cavernosum has not yet been accepted in the TNM 2002 [18].

Additionally, the measurement of the depth of invasion is recommended. Tumors with a mean depth of invasion of 4 mm and below do not progress whereas those with a mean depth of 9.8 mm progress [19]. Another very reliable marker of progression is vascular invasion. In controversial or suspicious cases the use of endothelial markers (CD31; CD34) to confirm or refute the invasion is suggested.

4.5. Other biomarkers of progression

Due to the rarity of penis cancer there are only few reports dealing with the prognostic value of biomarkers (Table 9). In the past only DNA cytometry, Ki-67 and p53 have been tested [20–22]. They have only a limited value for the assessment of the prognosis, but p53 seems to be very promising for the prediction of positive lymph nodes.

5. Conclusions

Because penile cancer is extremely rare in Europe the pathologists are not very familiar with the handling and reporting of this tumor. However, as with other urological malignancies the thorough and appropriate processing and reporting of the surgical specimens are mandatory for the prognostic assessment and therapy of penis tumors.

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