Tumors of the Penis and Scrotum

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Squamous Cell Carcinoma: General Features and Pathogenesis

Squamous cell carcinoma (SCC) is the most frequent penile tumor, occurring as usual-type SCC in almost 50 % of cases. It presents most frequently in the sixth to seventh decades of life [1], while it is uncommon in young adults. The different rates among countries and regional differences in prevalence even in the same country are not fully understood; the comparison of subtypes of penile cancer reported from high- and low-incidence regions showed no geographical differences between histologic subtypes and in the frequency of HPV-related tumors [2]. For instance, a similar distribution of penile cancer subtypes was observed in Paraguay and the USA, supporting the notion that previously reported geographical variations may have been the result of staging variation at clinical presentation, probably because lesions tend to be diagnosed early (i.e., in precancerous or in situ stages) in developed countries [2, 3]. The presence of human papillomavirus (HPV) was found to be a risk factor for penile SCC [4]: depending on the population examined, the technique used, and tumor morphology, the HPV detection rate has been estimated to range from 30 to 83 % of cases, while the prevalence is thought to be around 50 % [5]. In a recent immunohistochemical and HPV in situ hybridization (HPV ISH) study in a North American population, a low percentage (27 %) of high-risk HPV-positive cases of penile cancer was found [6]. In the majority of these cases, high-risk HPV subtypes (HPV-16 and HPV-18) were integrated into the genome with a characteristic nuclear ISH reactivity; the same integrated subtype was observed in both primary and metastatic tumors. HPV is most frequently associated with basaloid or warty carcinoma variants, where it has been reported in 75–100 % of cases, while the majority of usual/keratinizing and verrucous carcinomas are not HPV related [1, 2, 6–9].

Similar to what has been described for vulvar lesions, a bimodal pathogenesis for HPV-related and non-HPV-related cancers has been proposed [9–11]. Lichen sclerosus may represent a preneoplastic condition (see Chap. 12) in particular for some non-HPV-related cancers, i.e., verrucous, usual-type, papillary, and pseudohyperplastic

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carcinomas [12]. When we consider carcinomas affecting exclusively the foreskin, the association of lichen sclerosus with penile invasive carcinoma is much higher (69 %) [13]. Several other risk factors have been associated with the development of this cancer, including phimosis, smoking or chewing tobacco, chronic inflammation, tears, abrasions, balanitis, injuries to the penis, and poor hygiene [8, 9, 11]. A rare occurrence is the anaplastic transformation of verrucous carcinoma induced by radiotherapy [14].

Classification

A new morphological and molecular classification of the histologic types of penile SCC based on the presence of HPV has been presented in the latest edition of the WHO classification of urological tumors [15] (Table 13.1). For the aim of this textbook, we will focus on the spectrum of penile squamous cell carcinoma following the classification based on patterns of growth [9] according to an update of the 2004 World Health Organization classification [16].

Patterns of Growth

Superficial Spreading Growth Pattern

This pattern occurs when a slow-growing neoplasm associated with SCC of the usual type widely involves the superficial layers of the glans, sulcus, and/or foreskin. In 60 % of cases, more than one epithelial compartment is involved, while only 25 % of lesions are confined to the glans [9]. In the cut section shown in Fig. 13.1, the specimen consists of band-like white or gray-white tissue with thickening of the surface. There is an extensive in situ component (penile intraepithelial neoplasia, PeIN) intermixed with

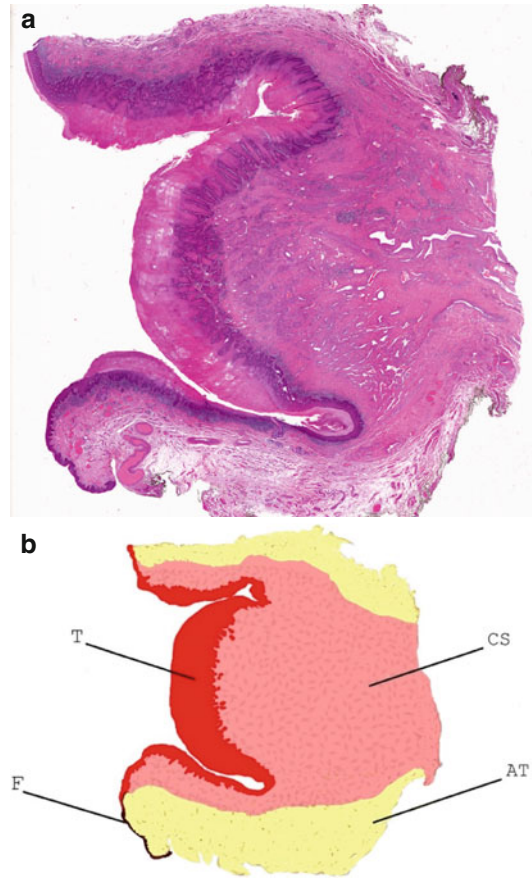

Fig. 13.1 Superficial spreading pattern of growth at low magnification. (**a**) Usual-type SCC involving the glans, sulcus, and foreskin with an in situ component and infiltration of the lamina propria. Careful examination of the surgical margins of the foreskin is mandatory to avoid recurrences. (**b**) Superficially spreading tumor (*T*) involves the glans, foreskin (*F*), and coronal sulcus, affecting the lamina propria and initially the corpus spongiosum (*CS*). *AT* adipose tissue

Table 13.1 Classification of penile squamous cell carcinomas according the HPV status

Non-HPV related	HPV related	Others
1. Usual	1. Basaloid	1. Mixed
2. Verrucous	2. Warty	2. Unclassified
3. Papillary NOS	3. Warty-basaloid	
4. Cuniculatum	4. Papillary basaloid	
5. Pseudoglandular	5. Clear cell	
6. Pseudohyperplastic	6. Lymphoepithelioma-like	
7. Adenosquamous		
8. Sarcomatoid		

minimally invasive carcinoma throughout the epithelium, with infiltration limited to the lamina propria. The superficial growth spreading to the foreskin warrants accurate examination of the surgical margins near the coronal sulcus, which should be examined in its entirety with circumferential sampling.

Vertical Growth Pattern

The cut surface of neoplasms with this pattern of growth shows deeply invasive carcinoma invading the corpus spongiosum with frequent penetration of the tunica albuginea and corpora cavernosa (Fig. 13.2a, b).

Almost 20 % of penile carcinomas are of this type, presenting as a large, fungating, and often ulcerated mass [9]. The more common histologic types associated with this pattern are basaloid, sarcomatoid, and high-grade usual SCC, and they often occur with regional lymph node metastases, carrying a poor prognosis.

Verruciform Growth Pattern

The glans is the most commonly involved site, with slow-growing proliferations that have a large, granular, exophytic surface (Fig. 13.3). Many tumors are low grade, infiltrating only the lamina propria. The most frequently associated histologic types are verrucous, warty (condylomatous), and papillary. Giant condylomata may show a similar pattern of growth (see Chap. 12).

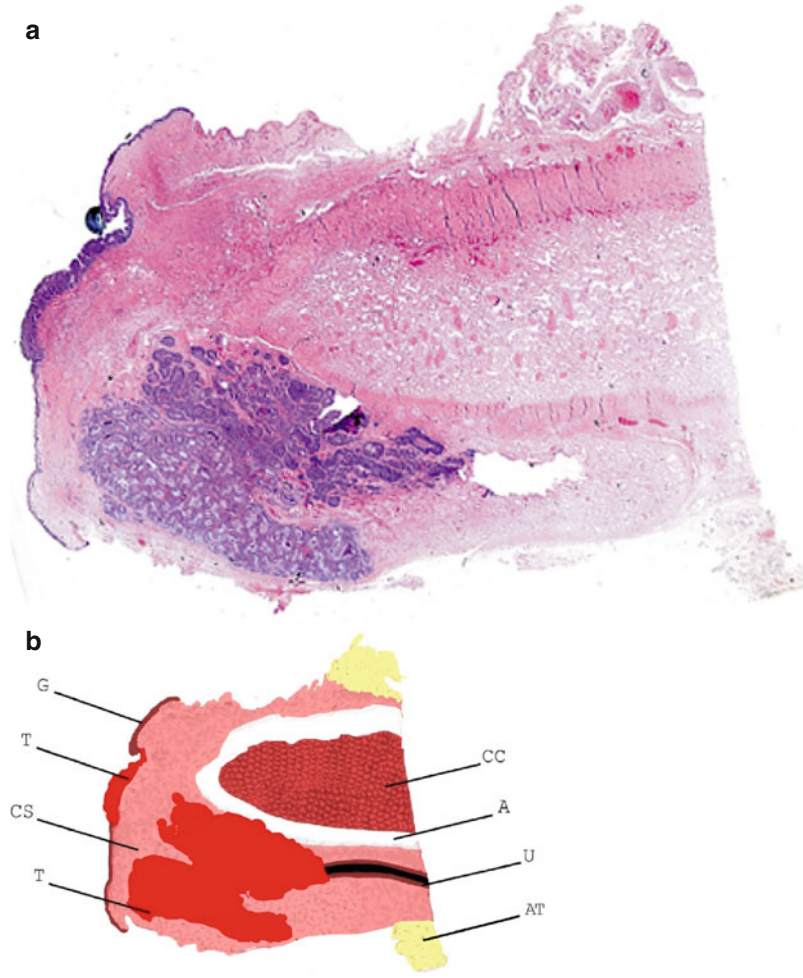

Fig. 13.2 Vertical pattern of growth. (**a**) Cut section showing a deeply invasive nodular ulcerated mass infiltrating the corpus spongiosum and tunica albuginea. (**b**) Vertical growth: tumor (*in red*) infiltrates corpus spongiosum and albuginea. In this section the corpus cavernosum is not infiltrated. *T* tumor, *G* epithelium of the glans, *CS* corpus spongiosum, *CC* corpus cavernosum, *A* tunica albuginea, *AT* adipose tissue, *U* urethra (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

Mixed and Multicentric Growth Patterns

Some penile tumors show two or three patterns of growth and are often at an advanced stage (10–30 % of all penile cancers). The most frequently reported histologic types are hybrid/verrucous and usual SCC. Less frequent is the occurrence of two or more independent foci of carcinoma separated by benign foci in a multicentric pattern. This growth pattern has been mostly reported in pseudohyperplastic carcinomas.

The recognition in penile biopsy specimens of the histologic types occurring with these different patterns of growth can guide the choice of the surgical procedure (i.e., partial versus radical penectomy); however, small biopsies often present objective limitations in their reliability to identify more or less aggressive subtypes and other important prognostic factors [17] (Fig. 13.4).

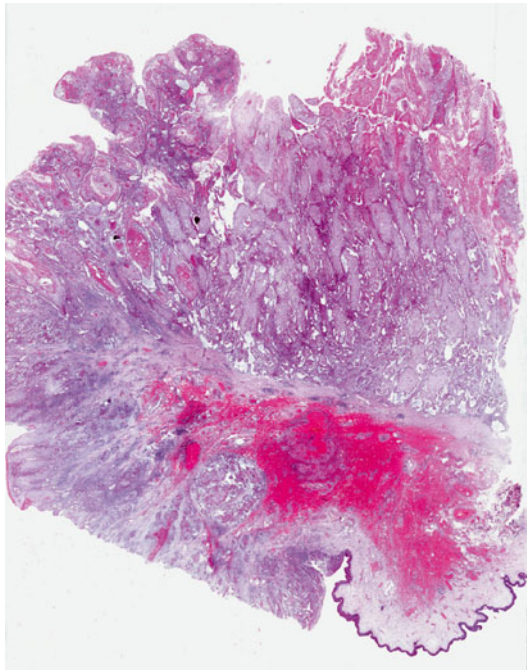

Fig. 13.3 Verruciform pattern of growth. Cut section of a carcinoma of the glans with verruciform pattern of growth

Squamous Cell Carcinoma, Usual Type

This is the most common histologic subtype of penile SCC (50–60 % of cases). The most frequent patterns of growth are vertical and superficial spreading patterns. Macroscopically, usual SCC presents as an exo- or endophytic, ulcerative, white-gray nodule. Accurate gross examination allows the detection of linear prominences (1–2 mm in thickness) in the mucous membrane adjacent to the invasive tumor, which microscopically appear as squamous hyperplasia or well-differentiated PeIN (Fig. 13.5a, b).

Fig. 13.4 Verruciform pattern of growth. This small biopsy shows a distinctive verruciform pattern of growth in a lesion with a low-grade appearance and microinvasion of the lamina propria. A conservative surgical approach is indicated in this case

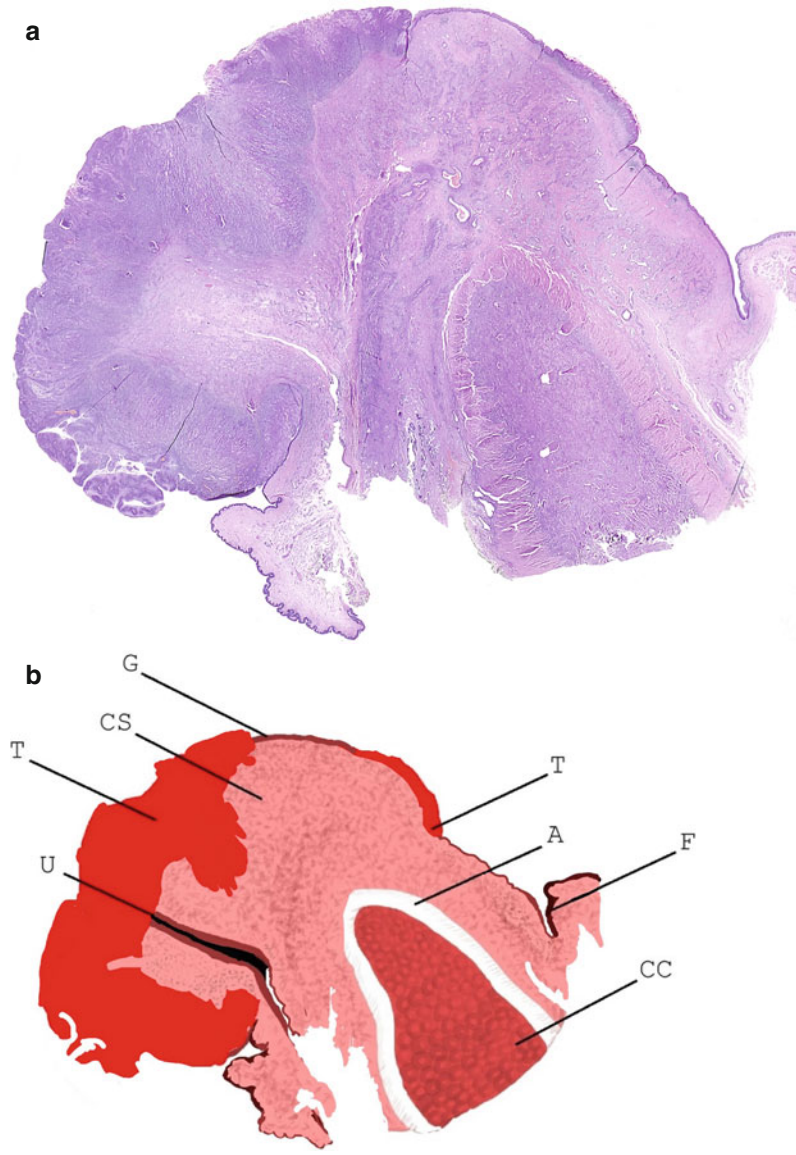

Fig. 13.5 Usual-type SCC. (**a**) Endophytic white-gray tumor infiltrating the corpora spongiosa with adjacent penile intraepithelial neoplasia and squamous hyperplasia in the mucosa of the glans. (**b**) Diagram of **a** *T* tumor, *G* squamous hyperplasia in the epithelium of the glans, *CS* corpus spongiosum, *CC* corpus cavernosum, *A* tunica albuginea, *U* urethra, *F* foreskin (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

Grading

Usual SCC is an infiltrating carcinoma that can be classified with a 3-grade system according to the level of keratinization, cellular pleomorphism, and the presence of regular nests or sheets of tumor cells.

Grade 1, *well differentiated*. The main features are sheets or nests of invasive carcinoma cells with central keratinization and keratin pearls (Fig. 13.6). It is less common than the other 2 grades, and its features sometimes overlap with pseudohyperplastic carcinoma.

Grade 2, *moderately differentiated*. The main features are smaller nests with scant keratinization and irregular outlines. There is limited pleomorphism; the cell nuclei are monomorphic with abundant cytoplasm. This grade is the most frequently observed, along with focal transition to grade 3 (Fig. 13.7).

Grade 3, *poorly differentiated*. The main features are nests, cords, and solid sheets of cells with

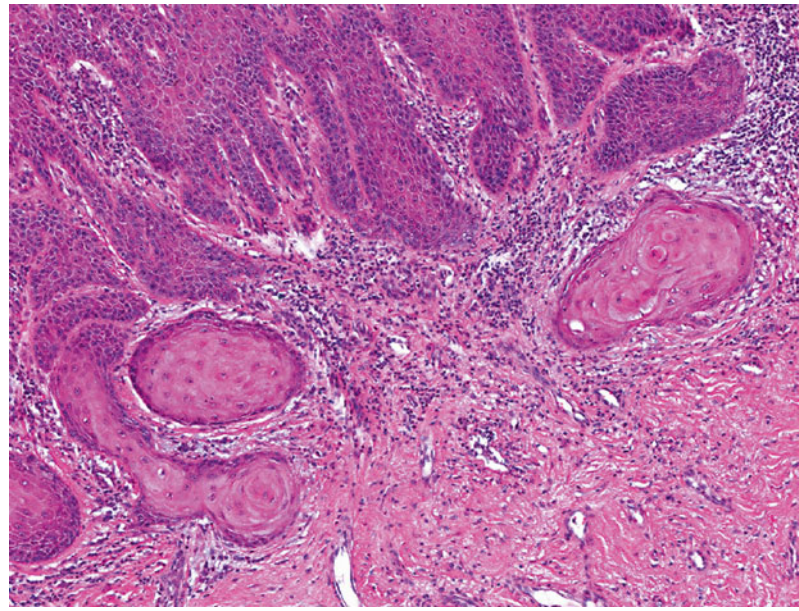

Fig. 13.6 SCC, grade 1. Well-differentiated grade 1 SCC showing extreme differentiation with large nests of tumor cells and keratin pearls

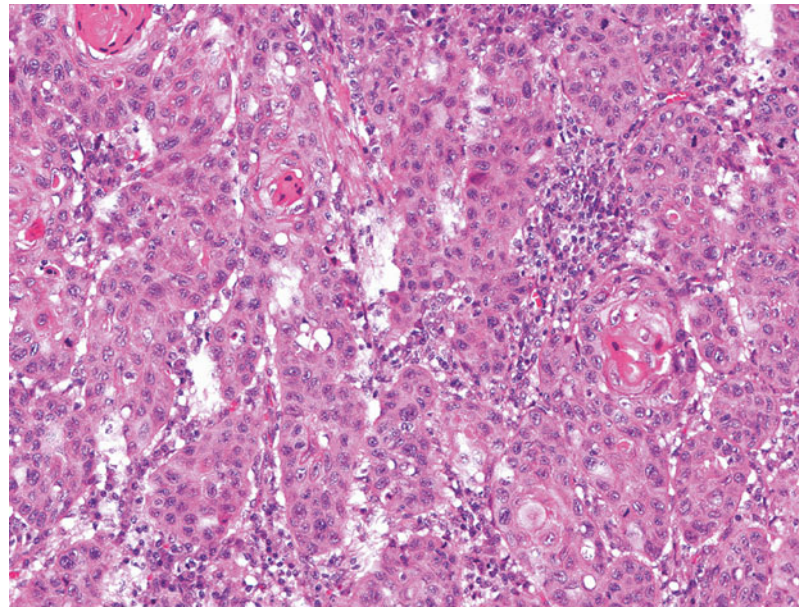

Fig. 13.7 SCC, grade 2. The cell nests are more irregular and smaller than in grade 1 SCC. There is pleomorphism and nuclear atypia. Keratin is commonly present

focal areas containing spindle, trabecular, and clear cells (Fig. 13.8).

Sarcomatoid change is considered a separate category, sometimes designated as grade 4, which often is combined with other tumor types and conveys a very poor prognosis.

The most difficult differential diagnosis is grade 3 SCC, due to its overlapping features with urothelial carcinomas and melanomas. Unusual patterns such as pseudohyperplastic, acantholytic, clear-cell, small-cell, and other patterns may be focally present [11, 16, 18].

A difficult to subclassify group of exophytic papillary lesions is collectively referred to as "verruciform neoplasms" (Table 13.2). Benign lesions such as giant condylomata (see Chap. 12) belong to this group as well as

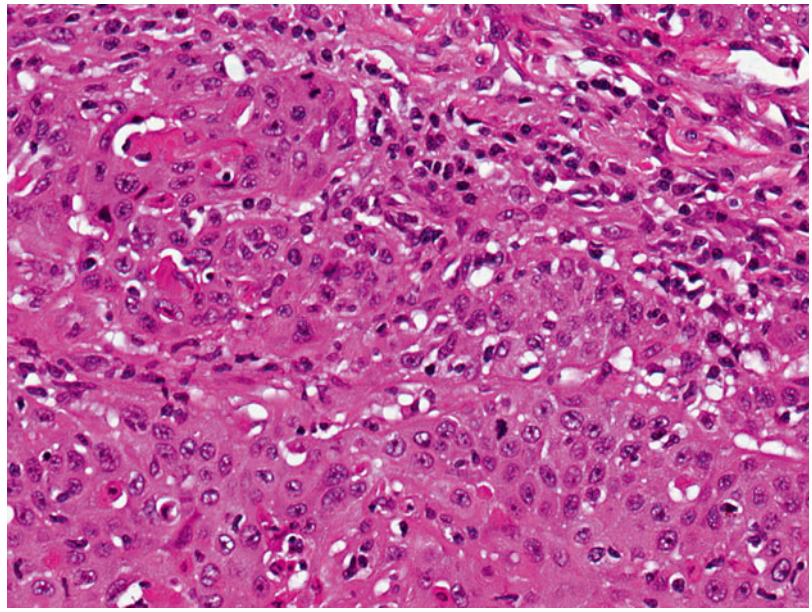

Fig. 13.8 SCC, grade 3. Poorly differentiated grade 3 SCC shows nonkeratinizing carcinoma with a solid pattern. Nuclear pleomorphism and mitoses are common features

Table 13.2 Verruciform penile tumors

1	Verrucous carcinoma	HPV unrelated; broad, pushing base; papillary surface without koilocytosis
2	Warty carcinoma	HPV related (HPV 16–18); irregular infiltrative base; koilocytosis throughout the papillomatous proliferations
3	Papillary carcinoma	HPV infection rarely detected; papillary surface; no koilocytosis
4	Carcinoma cuniculatum	Variant of verrucous carcinoma; deep invaginations
5	Condyloma acuminatum/giant condyloma	HPV related (low risk); koilocytosis limited to the surface

malignant tumors including warty "condylomatous" carcinoma, verrucous carcinoma, and papillary SCC.

Warty Carcinoma

Warty carcinomas are slow-growing lesions that may originate years before their histologic assessment. They are similar to vulvar neoplasms [19], and the first well-reported description in the penis can be found in the series of condylomata acuminata and related malignant lesions published in 1965 by Davies [20], who writes that "malignant condyloma occupies an intermediate position between giant condyloma and squamous cell carcinoma" [20]. Warty carcinoma presents as a large, firm, cauliflower-like mass with a white-gray surface, sometimes affecting multiple anatomical compartments. It has been found to encompass the glans, coronal sulcus, and foreskin as a cobblestone-like, firm mass (Fig. 13.9).

The gross appearance can be quite similar to that of condyloma acuminatum, but the nodularity is asymmetrical and frequently confluent. The cut surface of the penectomy specimen of Fig. 13.10a, b shows a papillomatous growth with penetration into the corpus spongiosum. The epithelium of the papillae appears as a whitish nodular growth with a dark core.

Microscopically there are complex papillae with pointed tips, irregular fibrovascular cores, and parakeratosis (Fig. 13.11). The nuclei are large and wrinkled, with frequent bi- or multinucleation and koilocytotic atypia. The changes are present at the surface of the papillae and also in invasive foci. Keratin-filled cysts are often present [21].

The tumor-stroma interface is usually irregular and infiltrative (Fig. 13.12). Mitoses are frequent and sometimes abnormal. Some warty carcinomas

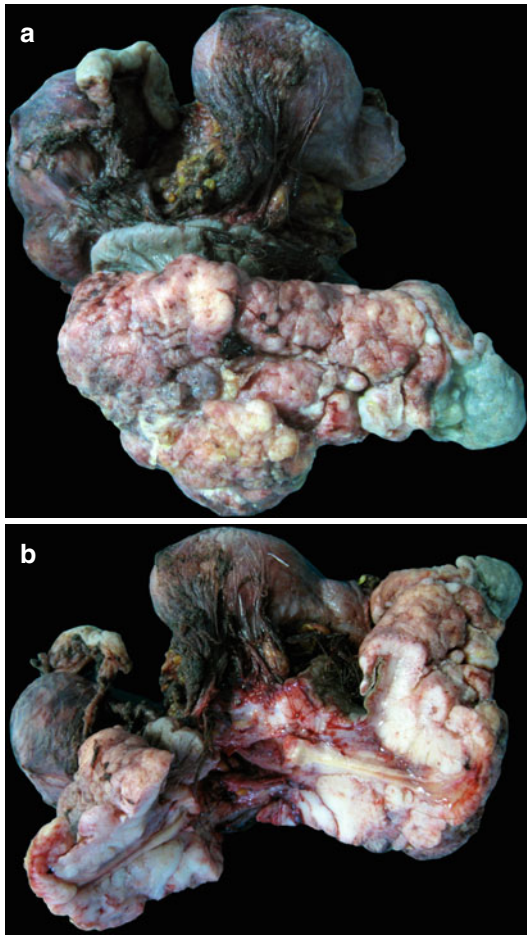

Fig. 13.9 Warty carcinoma. (**a**) Gross penectomy specimens showing an exophytic, cauliflower-like, white-gray mass with a cobblestone appearance. The involvement of the various anatomical levels is easily recognized on the cut section (**b**) in this advanced neoplasm (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

show clear-cell features (Fig. 13.13). The main differential diagnosis is with benign condyloma, which lacks the cellular pleomorphism seen in warty carcinoma [22]. In benign lesions the nuclear koilocytosis is confined to the superficial layers, while in warty carcinoma, it extends throughout the tumor. More challenging cases present as noninvasive, flat, papillary lesions in the glans. In this presentation the detection of high-risk HPV (usually subtype 16), which is typical of warty carcinoma, may be necessary to distinguish it from giant condyloma [23]. The reported incidence of HPV in warty carcinoma varies [4, 5, 21, 23–25]. The variability may be explained by different factors, including (a) viral DNA degradation in the preanalytic phase, (b) different sensitivity of the techniques used for HPV detection, and (c) selection of warty carcinomas based on nonuniform histopathologic criteria. Similar to other verruciform tumors, $p16^{INK4a}$ is the best immunohistochemical marker of warty carcinoma [24]. Verrucous and papillary carcinomas are low-grade verruciform neoplasms (see below) that are frequently misdiagnosed as warty carcinoma. Verrucous carcinomas are extremely well-differentiated proliferations without cytoplasmic clearing or koilocytic nuclear atypia. The epithelium-stroma interface lacks the irregular and infiltrative outline seen in warty carcinoma. The greatest diagnostic difficulty is with papillary carcinoma not otherwise specified (NOS), a hyperparakeratotic papillomatous proliferation with an irregular ("jagged") stroma-epithelium interface without koilocytosis. The clinical behavior of warty carcinoma is intermediate between that of the other types of low-grade verruciform tumors (papillary, verrucous) and usual SCC [1, 18, 21]. Local recurrence after penectomy has been reported in 10 % of cases and lymph node metastasis in 17–18 % [21].

Verrucous Carcinoma

Verrucous carcinoma is a slow-growing exophytic neoplasm which in its pure form accounts for 3–7 % of penile cancers [1, 14, 26]. In its classical occurrence, it is a 2–3 cm lesion of the glans, but it can also affect the foreskin or be multicentric. The use of strict microscopic criteria for its diagnosis allows a uniform classification of this unusual carcinoma, which in the past has been classified as Buschke-Löwenstein tumor or giant condyloma acuminatum [26]. The expression of $p16^{INK4a}$ and Ki67 is significantly lower in verrucous carcinoma than in usual-type SCC, while there is overexpression of p53 and Rb [27]. The reported low detection rate of HPV suggests that HPV infection has a limited oncogenic role in this

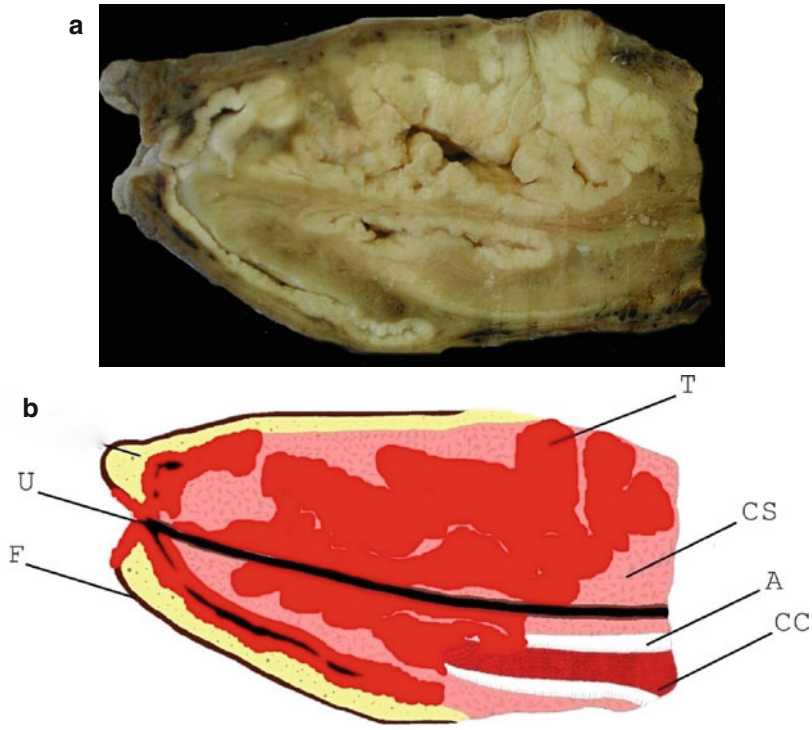

Fig. 13.10 Warty carcinoma. (**a**) Cut surface of penectomy specimen showing a papillomatous growth with an exophytic and endophytic growth pattern. There is irregular infiltration appearing as multiple, rounded lobules of tumor. The lesion extensively involves the foreskin, coronal sulcus, and glans. (**b**) Diagram of **a**. *T* tumor, *CS* corpus spongiosum, *CC* corpus cavernosum, *A* tunica albuginea, *F* foreskin, *U* urethra (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

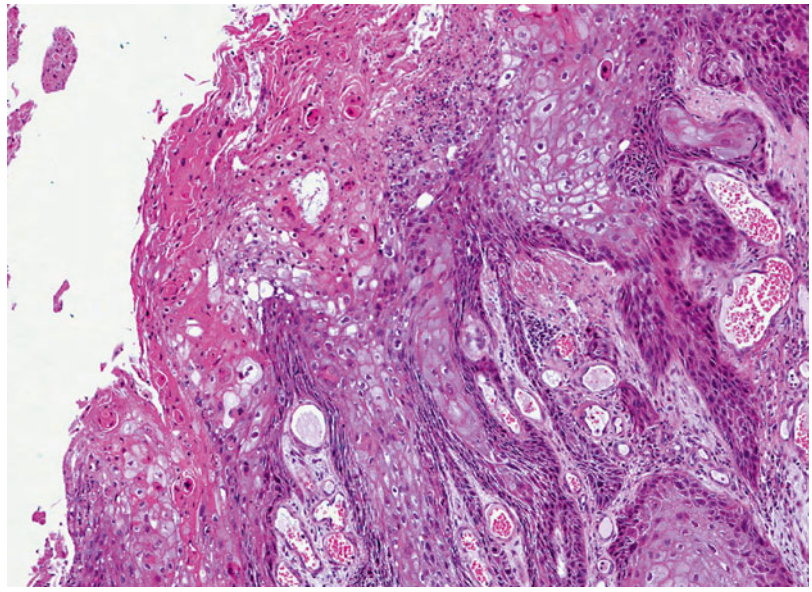

Fig. 13.11 Warty carcinoma. Prominent koilocytosis in the papillomatous growth of the tumor with parakeratosis in the superficial layers

histologic tumor type. Verrucous carcinoma can progress locally, but distant metastases are very infrequent [26, 28]. Macroscopically it presents as an exophytic, white-grayish lesion with a superficial verruciform appearance. Less than one-fourth of cases are deeply invasive into the corpora cavernosa, and the front of invasion shows a sharply delineated interface between the

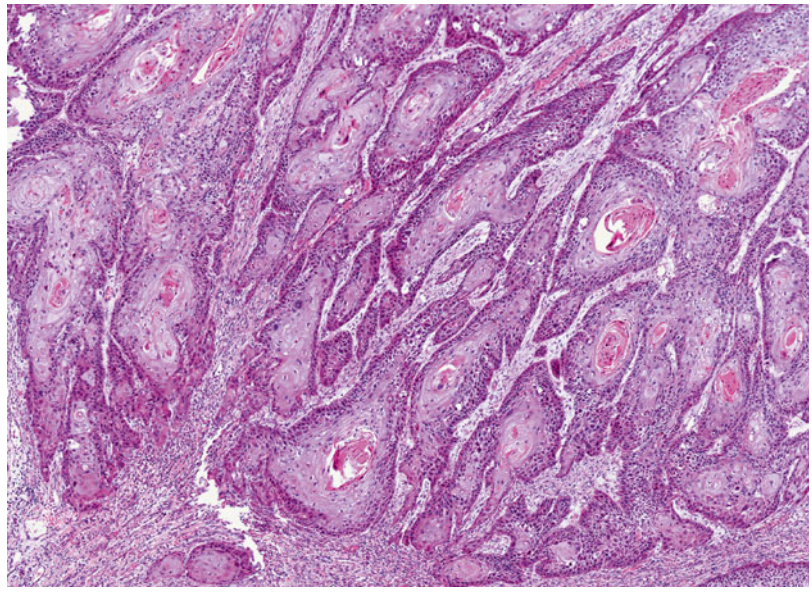

Fig. 13.12 Warty carcinoma. Same case as Fig. 13.11, with an irregular and infiltrative tumor-stroma interface composed of small irregular nests with atypia. Koilocytotic changes are present in the infiltrating cell nests of this well-differentiated carcinoma

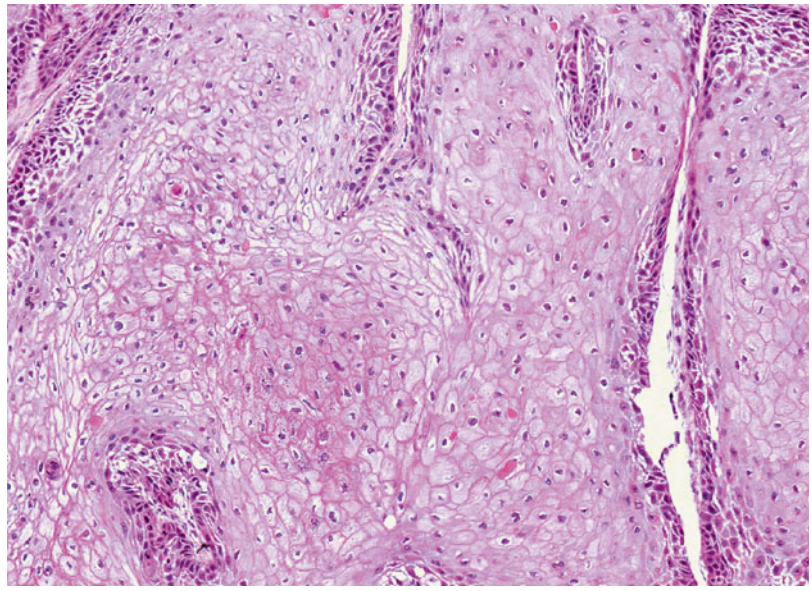

Fig. 13.13 Warty carcinoma. Clear-cell features with some crinkly nuclei

neoplasm and the lamina propria. Microscopically the lesion is well differentiated with hyperkeratosis, papillomatosis, and acanthosis (Figs. 13.14 and 13.15). The tumor cells show prominent intercellular bridges with no atypia. The bases of the squamous tongues are broad, with pushing, regular borders (Fig. 13.16). Few mitoses are present. Unlike condylomatous papillae, the papillae in verrucous carcinoma are not arboriform; they lie close to each other, show keratin plugs in the center, and are without central fibrovascular cores (Fig. 13.15). In the adjacent mucosa, there is squamous hyperplasia, lichen sclerosus, or well-differentiated PeIN [12]. The main differential diagnoses are verrucous hyperplasia and mixed SCC; hyperplastic lesions are smaller and the broad base lacks the downward growth of the bulbous squamous projections

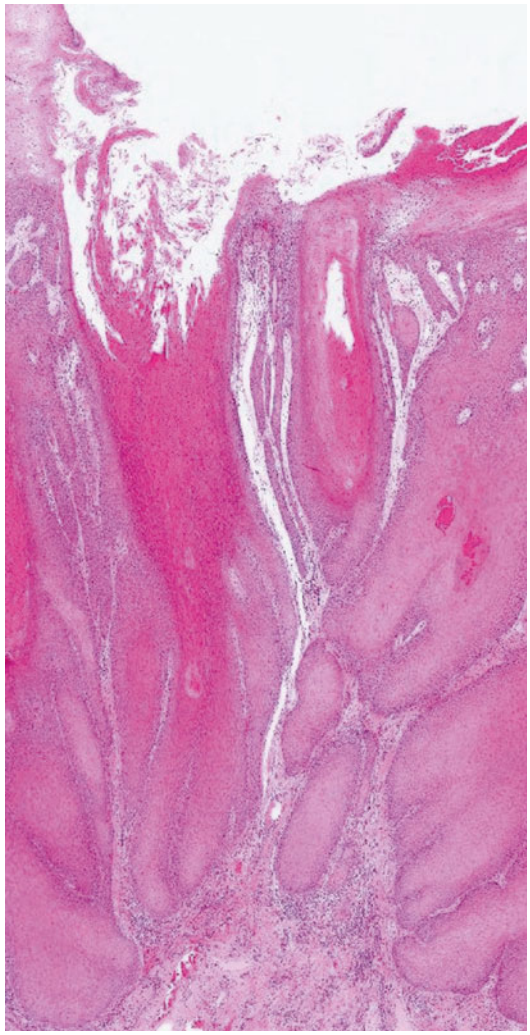

Fig. 13.14 Verrucous carcinoma. Hyperkeratosis, papillomatosis, and acanthosis with a broad base on the corpus spongiosum

observed in the carcinomatous counterpart. Mixed SCCs consist of usual-type areas intermingled with verrucous carcinoma. Papillary SCC has more cellular atypia and has an irregular front of invasion that is easy to distinguish. Regional lymph node or distant metastasis does not occur in typical cases of verrucous carcinoma [9], and given its low malignant potential, partial or local excision is the treatment of choice. The mortality rate of pure verrucous carcinoma is zero [1, 9, 18]. On the basis of a preoperative biopsy that is diagnostic of verrucous carcinoma, prophylactic lymphadenectomy is not recommended [29].

Papillary Squamous Cell Carcinoma

Papillary SCC NOS is the third distinctive type of low-grade verruciform neoplasms of the penis [30]. The macroscopic presentation in the penectomy specimen shows an exophytic papillomatous tumor with extensive superficial involvement of the glans, coronal sulcus, and foreskin. The most common microscopic distinguishing features compared with verrucous SCC are the complex papillae with irregular fibrovascular cores; typically the tips of the papillae are polymorphic (straight, blunt, rounded, spiky, etc.) (Fig. 13.17). Papillary SCC lacks the viral changes seen in warty carcinoma, while there is more nuclear atypia than in verrucous SCC; the HPV detection rate is very low or even zero [4, 16, 30, 31]. The tumor-stroma interface is jagged and the frequency of deeper infiltration into the corpora cavernosa is higher (25–33 %) than in verrucous carcinomas [9, 11, 16, 30]. Many associated lesions have been reported, with a prevalent occurrence of squamous hyperplasia with differentiated PeIN.

Papillary carcinoma has low-grade histology and a metastatic rate similar to warty carcinoma, but it generally has a good prognosis: the recurrence rate is about 12 %, and the rates of inguinal lymph node metastases and mortality both range from 0 to 12 % [9]. Unlike other verruciform tumors (warty, verrucous, and cuniculatum carcinomas), the papillary pattern may superficially be part of basaloid or warty-basaloid invasive carcinoma. This unusual tumor, similar to urothelial carcinoma (see Fig. 12.13), is composed of papillae with fibrovascular cores lined by poorly differentiated cells and, being an HPV-related neoplasm of the family of basaloid carcinomas, shows characteristic p16-positive immunostaining that lacks in papillary carcinoma [32] (Table 13.2).

Carcinoma Cuniculatum

This very unusual tumor is similar to verrucous carcinoma at the surface, but its hallmark is the presence of extensive infiltration of erectile tissues with the formation of sinuses and cyst-like tracts (Fig. 13.18) [33]. Fistulae opening to the foreskin or penile shaft are frequently observed and are comparable to those in plantar epithelioma cuniculatum

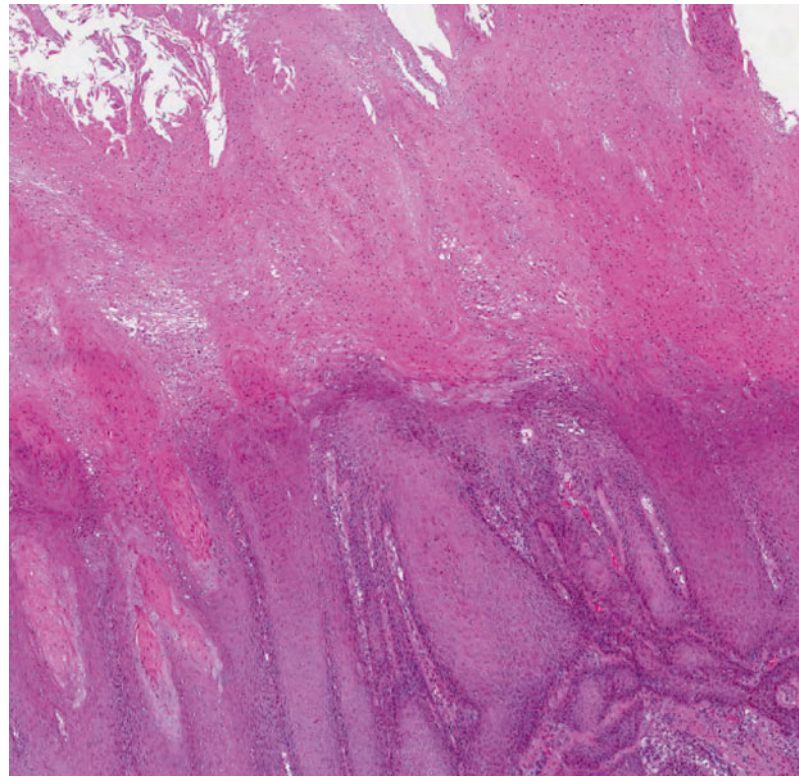

Fig. 13.15 Verrucous carcinoma. The papillae are not arboriform, and they lack fibrovascular cores. There are keratin plugs in the center. The tips of the papillae show hyperkeratosis

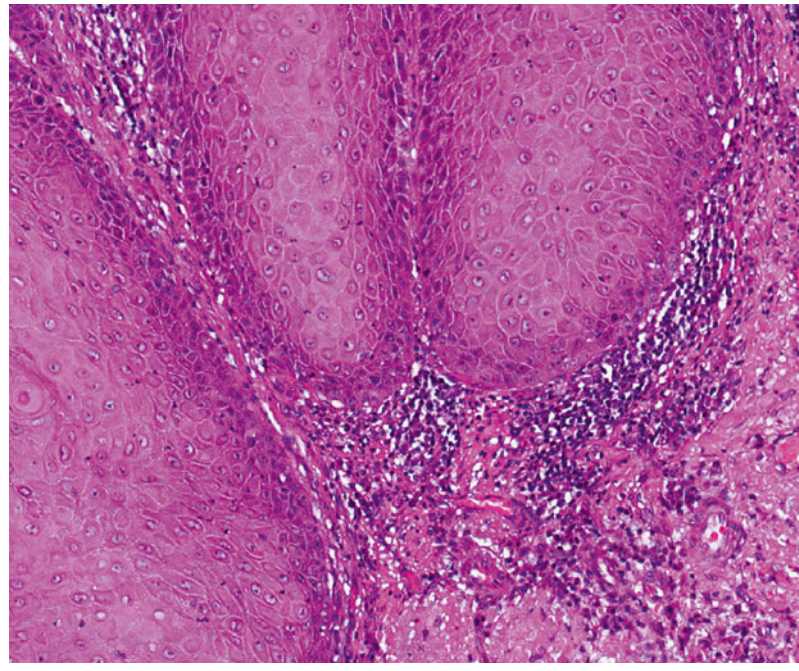

Fig. 13.16 Verrucous carcinoma. The tumor base has broad bulbous fronds of extremely well-differentiated squamous cells with broad pushing margins. The dermal-tumor interface shows an apparently intact basement membrane and absence of an active basal layer

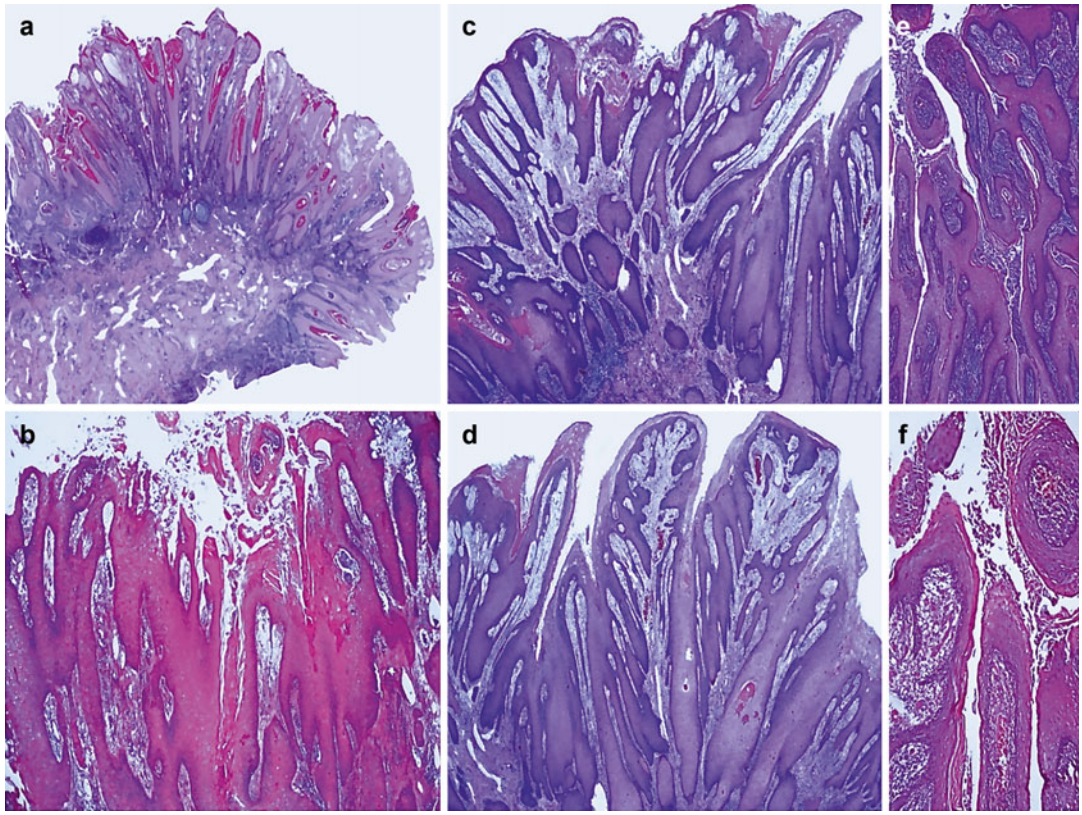

Fig. 13.17 (**a**–**f**) Papillary carcinoma. Complex papillae lacking viral changes and with absent atypia in a papillary carcinoma (Courtesy Prof. Antonio Cubilla)

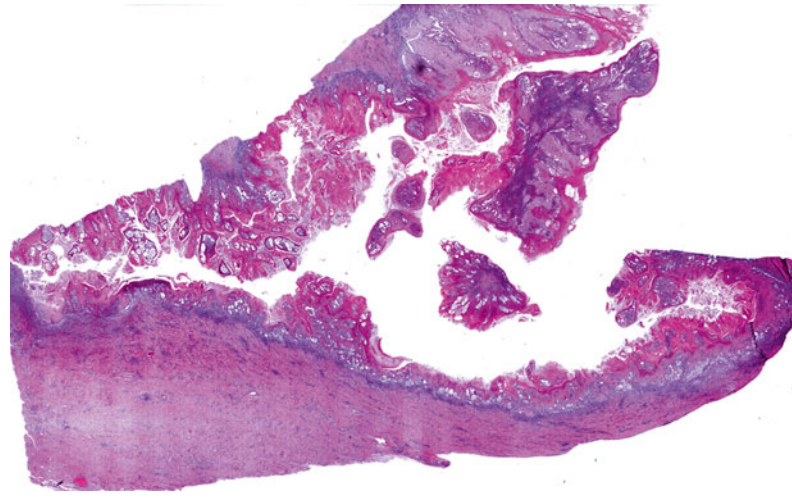

Fig. 13.18 Carcinoma cuniculatum. Low power view of a cut-section. Note the endophytic burrowing channels, the pseudocystic space and interanastomotic and complex pattern of the lesion

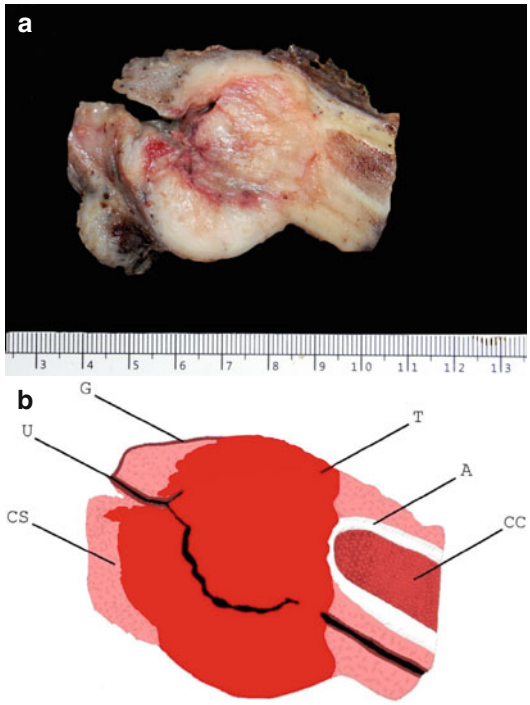

Fig. 13.19 Sarcomatoid carcinoma, gross specimen. (**a**) A polypoid solid mass ulcerates the surface of the glans, extensively involving the corpus cavernosum. (**b**) Diagram of **a**. *T* tumor, *G* epithelium of the glans, *CS* corpus spongiosum, *CC* corpus cavernosum, *A* tunica albuginea, *U* urethra (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

[34, 35]. The prognosis is similar to that of verrucous carcinoma; of the cases reported in the literature, none metastasized.

Sarcomatoid Carcinoma

The relatively uncommon occurrence of sarcomatoid carcinoma in the genitourinary tract [36] is confirmed by its low prevalence among penile tumors. Sarcomatoid carcinomas account for approximately 4 % of penile carcinomas. They are a high-grade, most likely HPV-unrelated variant of SCC characterized by biphasic neoplasia predominantly composed of spindle cells (>50 %) [9]. The gross appearance of most tumors is a large, polypoid, fungating, and frequently ulcerated mass affecting the glans, with a vertical pattern of growth deeply infiltrating the corpora cavernosa (Fig. 13.19a, b); also the foreskin is frequently infiltrated. The presence of corporal intrapenile metastasis (so-called satellitosis), an unusual type of cancer progression [37], has been identified in the corpora cavernosa and the skin. Poorly differentiated spindle cell proliferation arising from the epithelium of the distal penis most likely represents a sarcomatoid carcinoma (Fig. 13.20), although the connection with the lining epithelium

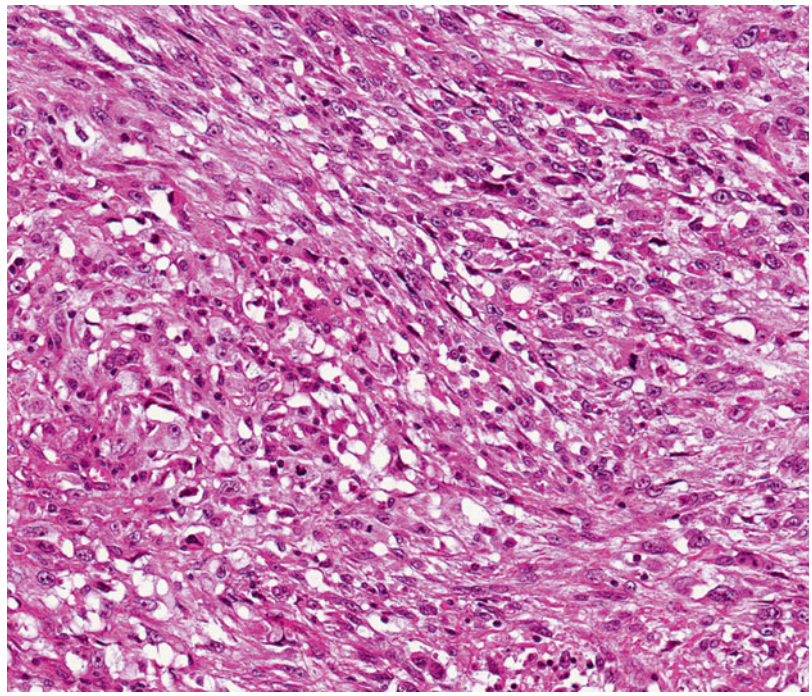

Fig. 13.20 Sarcomatoid carcinoma. Spindle cell features are present. This tumor area simulates a leiomyosarcoma

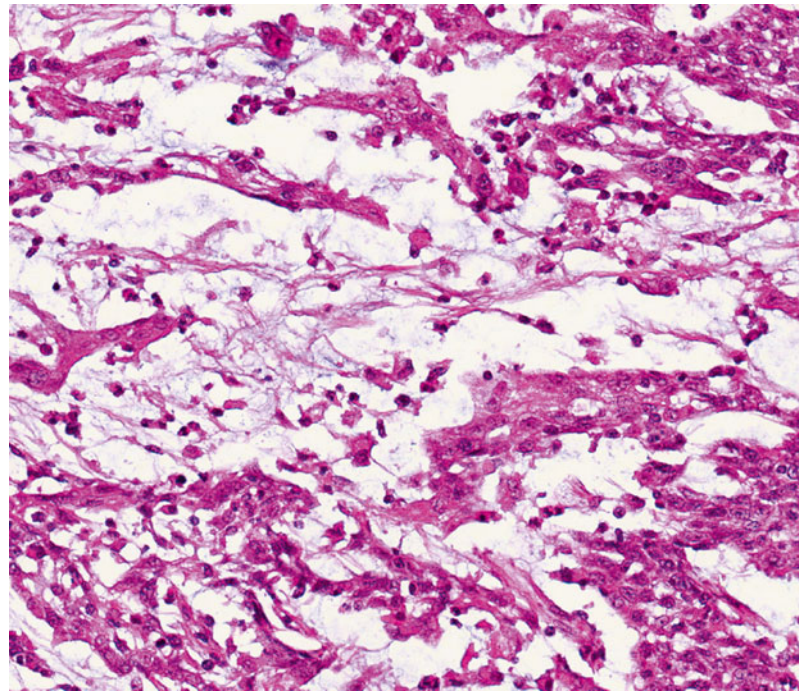

Fig. 13.21 Sarcomatoid carcinoma, microscopic appearance. Spindle cell proliferation in myxoid stroma simulating a myxoid sarcoma

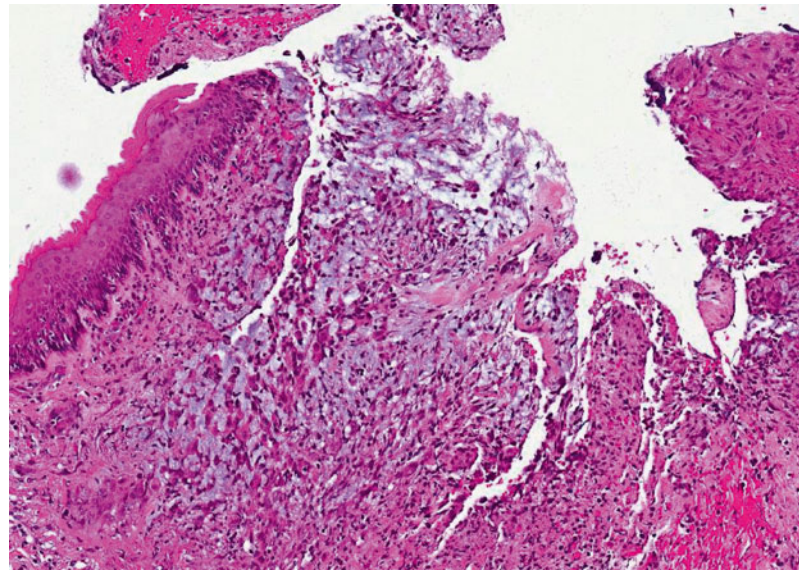

Fig. 13.22 Sarcomatoid carcinoma, microscopic appearance. Sarcomatoid carcinoma in myxoid matrix ulcerating the epithelium of the foreskin

may be difficult to assess even after extensive sampling. For this reason, despite the lack of a connection with the epithelium of the glans or the absence of high-grade PeIN, a large spindle cell tumor ulcerating the distal penis represents in the majority of cases sarcomatoid differentiation in an SCC. The spindle cell component is frequently disposed in interlacing bundles or embedded in a loose myxoid stroma resembling fibrosarcoma or leiomyosarcoma (Figs. 13.21 and 13.22). Other areas may have angiosarcomatoid features, while heterologous elements (cartilaginous tissue, bone, strap cells corresponding to striated muscle with rhabdomyomatous features) have rarely been reported. Instead, pleomorphic giant cells and multinucleated cells are frequent. The differential diagnosis includes different kinds of sarcomas and melanomas, but penile sarcomas are located in the

deep penile shaft, an uncommon site for penile carcinoma. Squamous differentiation and immunohistochemical positivity for p63 cytokeratins and 34βE12 are specific markers to categorize these tumors as epithelial (Fig. 13.23).

Patients with sarcomatoid carcinomas have a poor prognosis, and the survival is usually short (less than 1 year) [38]. The lymph node metastasis rate is very high (75–89 %) and local and systemic recurrence is common (67 %) [9]. The spindle cell component may be observed in a recurrent tumor with previous nonsarcomatoid differentiation, as in the case of verrucous carcinoma with anaplastic transformation following radiotherapy [14]. These tumors convey a very poor prognosis.

Basaloid Carcinoma

Basaloid carcinoma (BC) is an aggressive tumor occurring as a large, ulcerated mass with endophytic, vertical growth deeply penetrating the corpora cavernosa. It is generally composed of a monotonous population of small- to medium-sized cells with basophilic cytoplasm [9, 39]. The pattern of solid nests of small cells is predominant, while focal basaloid features may be seen in association with other penile tumor subtypes [40]. The solid pattern of growth with small, poorly differentiated cells with scant cytoplasm resembles basal cell carcinoma (BCC) of the vulva [19]. The preferred site of origin of BC is the glans. The most frequent pattern is vertical growth (nodular) (Fig. 13.24), but some cases with a superficial spreading pattern have been reported. The nests are composed of anaplastic and small cells with round to oval nuclei, and mitoses are frequently observed (Figs. 13.25 and 13.26); high-power magnification shows uniform ovoid basaloid cells with inconspicuous nucleoli and central comedonecrosis with a mixture of necrotic debris and keratin material. Other, more unusual, microscopic features are spindle cell features, a "starry sky" appearance due to individual cell necrosis, and interstitial hyalinization. In the majority of BC cases, carcinoma in situ (CIS) is present adjacent to invasive carcinoma [39] (Figs. 13.24 and 13.27). The 16^{INK4a} immunostain is usually positive in intraepithelial and invasive BC (Fig. 13.28) [41]. A common finding is lymphovascular and perineural invasion, while a large-cell pattern with more pleomorphic nuclei is observed rarely. Another uncommon occurrence is papillary BC, a superficial papillary tumor composed of papillae with small basophilic cells resembling papil-

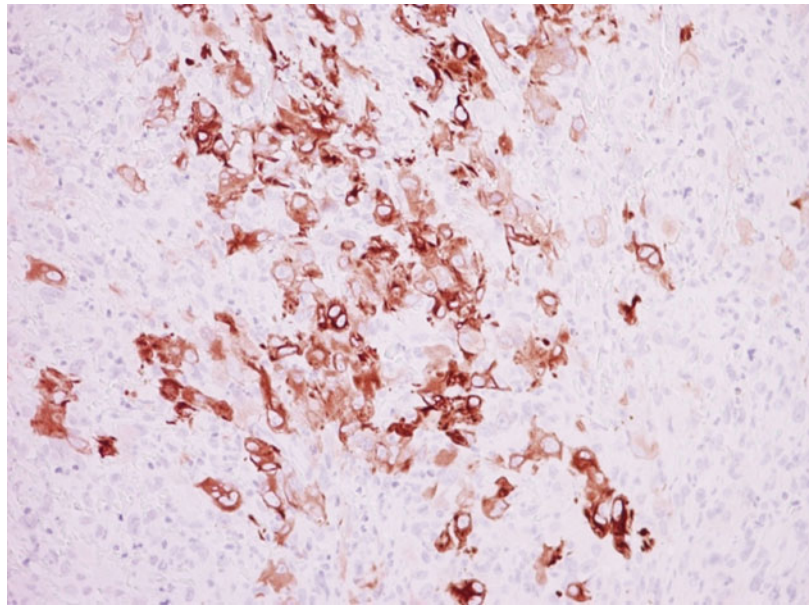

Fig. 13.23 Sarcomatoid carcinoma. Rare spindle cells immunostained by cytokeratin pool

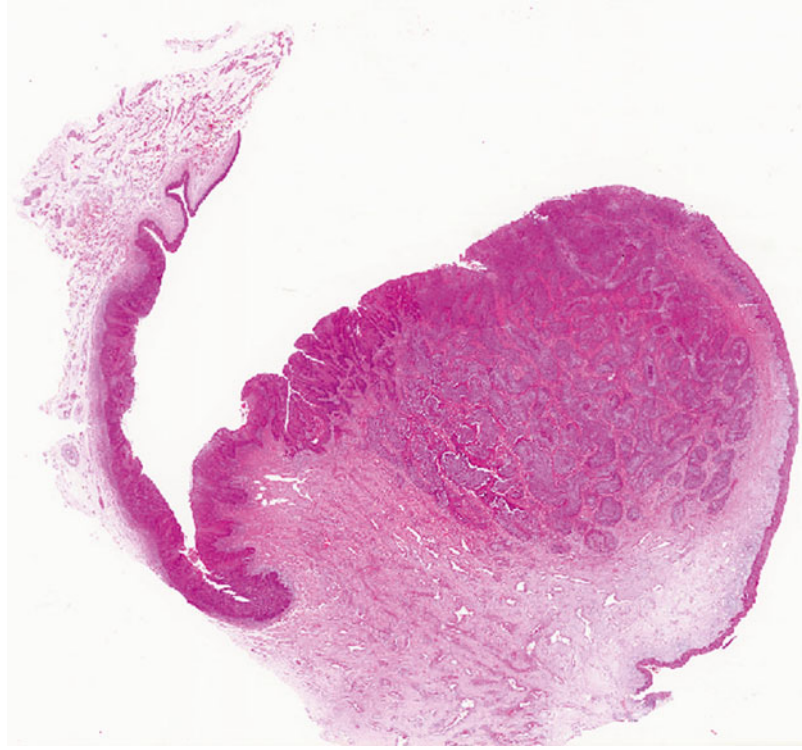

Fig. 13.24 Basaloid carcinoma. Neoplasm with a prevalent basaloid component with vertical growth pattern and in situ component (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

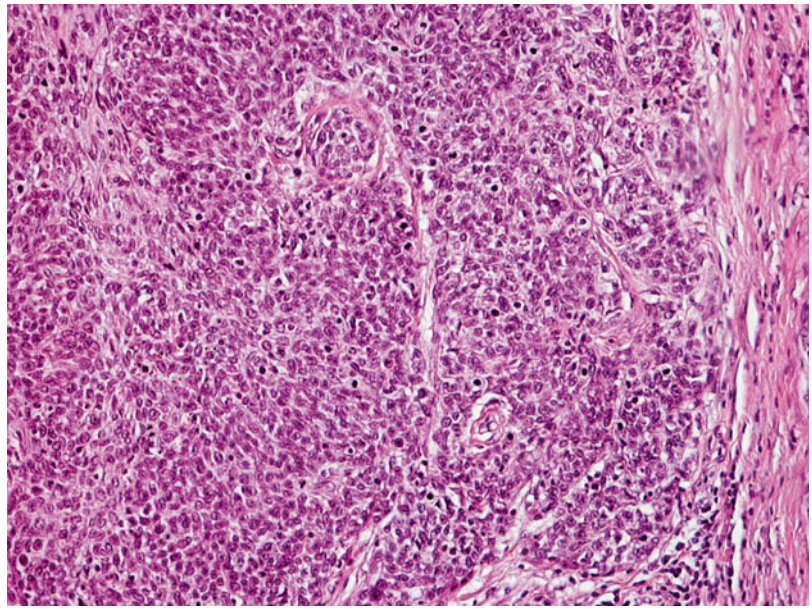

Fig. 13.25 Basaloid carcinoma. Solid nests consisting of basophilic small ovoid basaloid cells with small nucleoli and numerous mitoses

lary urothelial carcinoma [42]; this neoplasm is usually HPV related and immunoreactive to p16. HPV positivity has been reported in a high percentage of BCs, ranging from 71 to 80 % [4, 24, 43]. The presence of squamous cell differentiation in less than 20 % of the tumor is reported in the mixed subtype classified as mixed squamous-basaloid carcinoma.

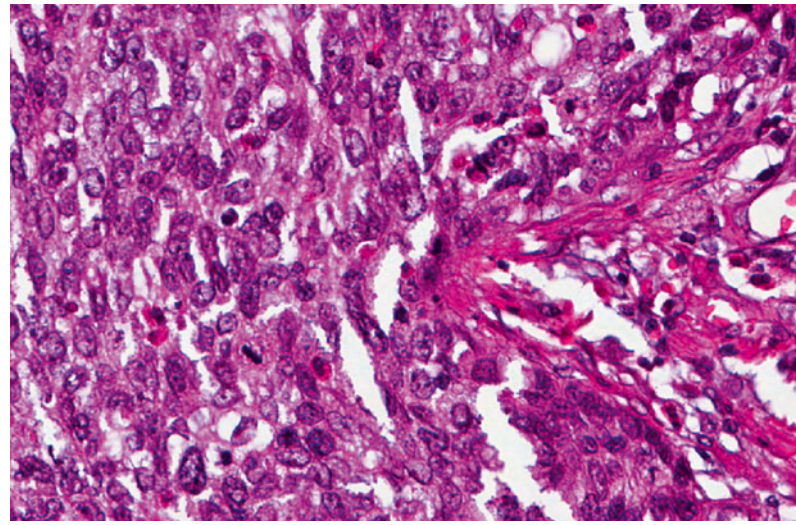

Fig. 13.26 Basaloid carcinoma. Basophilia in a poorly differentiated basaloid carcinoma with numerous mitoses

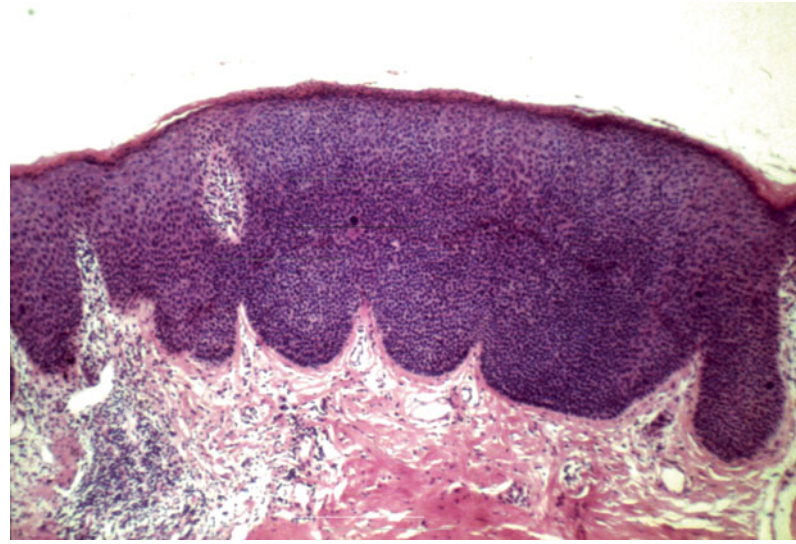

Fig. 13.27 In situ basaloid carcinoma. Most of the carcinoma in situ is uniformly composed of small immature cells

BC has a high incidence of nodal metastasis, with more than 50 % of cases showing regional metastasis at presentation [18, 39]. Recurrences have been reported in one-third of cases [39]. The mortality rate due to systemic spread is very high (>60 %), and particularly tumors deeply infiltrating the corpora cavernosa with a >10 mm diameter carry a bad prognosis [39].

The main differential diagnoses are (a) high-grade usual-type SCC, (b) BCC of the skin, (c) urothelial urethral carcinoma, and (d) small cell neuroendocrine carcinoma. Usual-type SCC shows pleomorphic cells with abundant keratinized cytoplasm, while BC shows uniform nests of small cells throughout the tumor and keratinization is confined to the central area. BCCs usually originate in the skin of the shaft and are more frequently observed in the scrotum. Urothelial urethral carcinoma most frequently occurs adjacent to CIS or papillary carcinoma in the urothelial mucosa, and absence of p16 immunostaining and positivity for GATA3 support the urothelial origin. Neuroendocrine carcinoma, in particular metastasis of Merkel cell carcinoma, has organoid, ribbon/trabecular features that are absent in BC. Immunohistochemical staining for

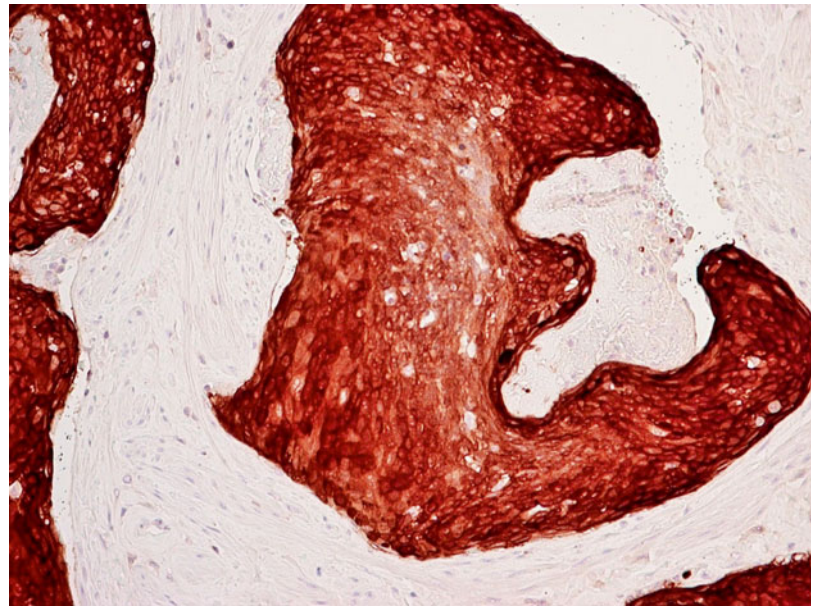

Fig. 13.28 p16 immunostaining in basaloid carcinoma. Solid aggregate of cells in basaloid carcinoma showing p16 immunostaining

CK20 and neuroendocrine markers is sometimes necessary for a definitive diagnosis.

Pseudohyperplastic Carcinoma

This is a recently described variant of low-grade SCC, preferentially affecting the foreskin and occurring at a more advanced age than usual-type SCC. It is an extremely well-differentiated, nonverruciform neoplasm strongly associated with the occurrence of lichen sclerosus in a similar way to other variants of SCC exclusive to the foreskin and characterized by low grade and multicentricity [13]. In a series of ten cases reported by Cubilla et al. [44], the authors named this unusual variant "pseudohyperplastic SCC." The name emphasizes the difficulty in distinguishing it from pseudoepitheliomatous hyperplasia, especially in small biopsies. In partial penectomies the infiltration of the corpus spongiosum or dartos is a distinguishing feature of carcinoma, which shows a stromal reaction around the infiltrative nests. Macroscopically, pseudohyperplastic carcinoma is flat or slightly elevated, often multicentric, restricted to the mucosa, and measuring less than cm 3 in diameter. Microscopically, the downward proliferation of well-differentiated carcinoma shows superficial infiltration of the lamina propria and preputial dartos (Fig. 13.29). The nests rarely show keratinization; the absence of papillomatous growth, observed in papillary carcinoma, and the irregular interface with the underlying stroma allow the differentiation from verrucous carcinoma. The good prognosis of this variant is related to its low-grade and superficial invasion of the corpora spongiosa. Other noninfiltrative lesions commonly observed in the adjacent mucosa are squamous hyperplasia, flat hyperplasia, and – less commonly – verrucous hyperplasia. No inguinal node metastases are reported in this entity.

Pseudoglandular Carcinoma

This is a highly unusual variant of SCC characterized by pseudoglandular spaces partially filled with eosinophilic debris containing squamous cells, keratin, and microabscesses (Fig. 13.30) [45]. At low magnification a multicystic or honeycomb appearance is the predominant feature with amorphous material in the lumen (Fig. 13.31). Synonyms are acantholytic SCC and adenoid SCC, used for neoplasms with more than 30 % of the tumor volume showing pseudoglandular features. Recently, an unusual pseudoangiomatoid variant was described in a

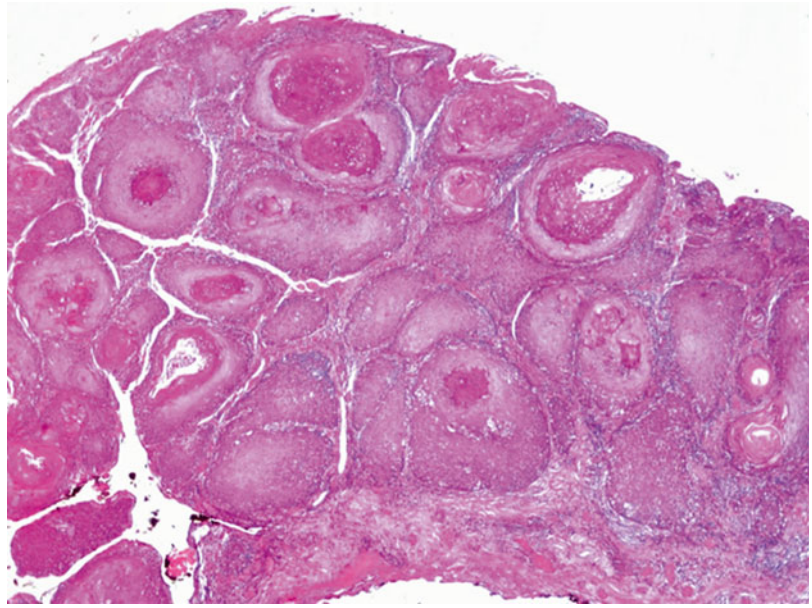

Fig. 13.29 Pseudohyperplastic carcinoma. Downward proliferation of well-differentiated carcinoma showing nests infiltrating the lamina propria

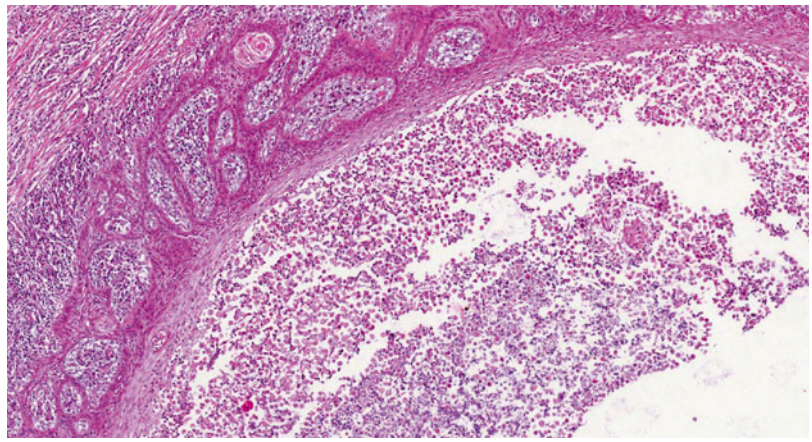

Fig. 13.30 Pseudoglandular SCC. Pseudoglandular spaces filled with eosinophilic debris, squamous cells, keratin, and inflammatory cells

middle-aged patient who died 6 months after penectomy with widespread lung metastases (Fig. 13.32a, b) [46]. Poor prognosis of pseudoglandular SCC is common to all reported series, with a mortality rate higher than 70 % [45].

Adenosquamous Carcinoma

This unusual neoplasm, probably originating in the penile surface epithelium, has the macroscopic appearance of an exophytic, yellow-gray, firm, granular mass. Microscopically it shows glands of small to medium size containing intraluminal secretory material. Often there is mucinous, alcian-positive material in the lumen. The remainder of the mass shows squamous differentiation, contributing to the biphasic appearance of this tumor. The preferential site is the perimeatal glans, but extension to the coronal sulcus and foreskin has been reported [47]. CEA immunostaining is typically observed in the glandular component. Local recurrence has been observed in up to 25 % of cases and inguinal node metastases in 43–50 % [48].

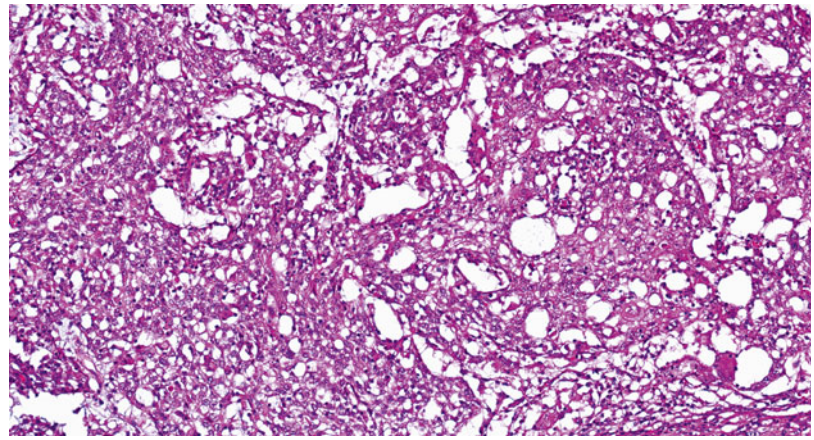

Fig. 13.31 Pseudoglandular SCC. Predominant multicystic microscopic feature corresponding to the acantholytic appearance of the tumor

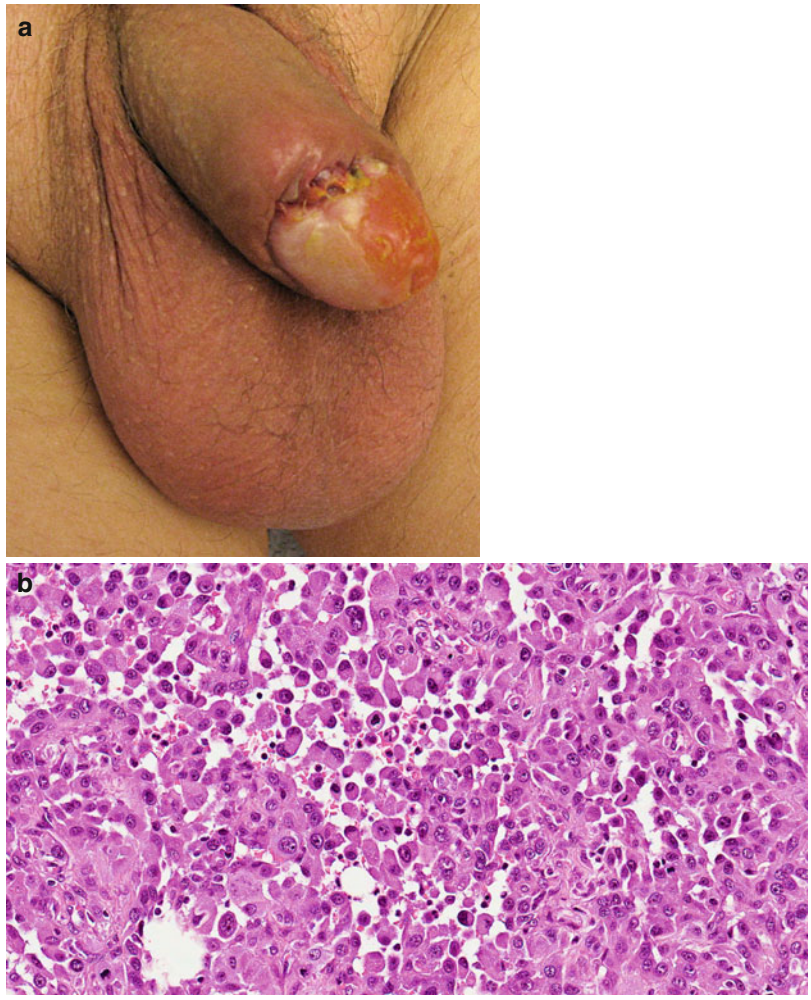

Fig. 13.32 Pseudoglandular carcinoma, pseudoangiomatoid variant. Unusual presentation of pseudoangiomatous pattern in a pseudoglandular (acantholytic) carcinoma. The lesion occurred in the glans (**a**) as a crusted, flat lesion that metastasized to the lung after radical penectomy. (**b**) Neoplastic cells with epithelioid cell features are dispersed in a pseudovascular space

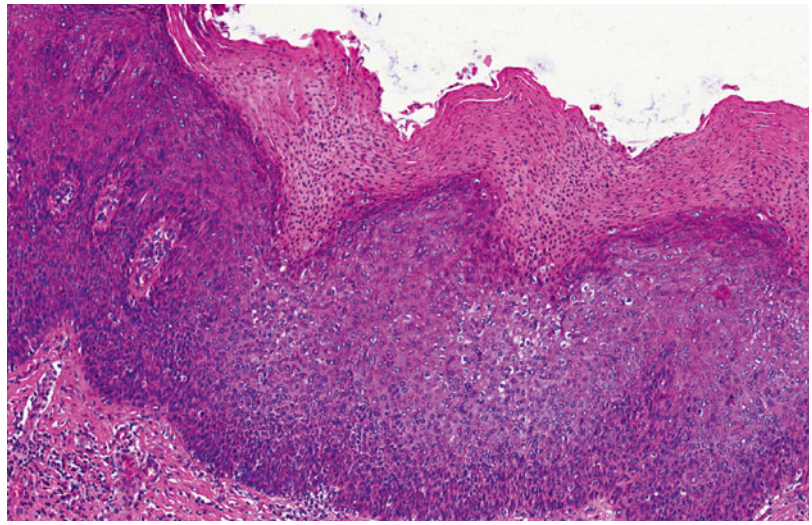

Fig. 13.33 Warty-basaloid PeIN. Penile intraepithelial neoplasia showing warty-basaloid features (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

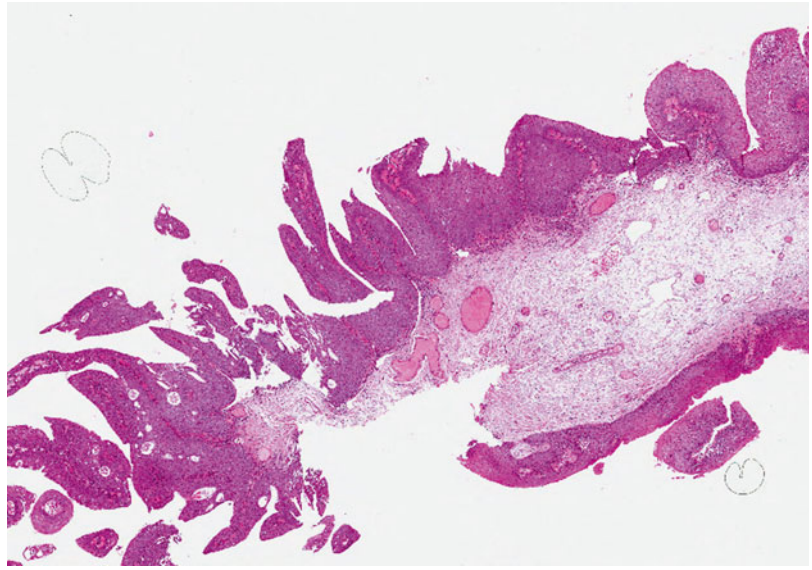

Fig. 13.34 Mixed carcinoma. Papillary growth in a tumor with prominent condylomatous changes

Mixed Carcinomas

Mixed penile tumors harbor more than one histologic subtype and each of the subtypes should make up at least 20 % of the tumor mass [2, 9]. Their frequency ranges between 20 and 33 % of all penile carcinomas. Most of these tumors are located in the glans. Macroscopically the superficial verruciform neoplasm is often admixed with a vertical pattern as observed in the basaloid subtype or in poorly differentiated SCC and in the most common mixed carcinoma: warty-basaloid SCC [49, 50]. This tumor has more than 10 % of basaloid cells that are located in superficial papillae or the deep front of invasion or in both areas. The same histologic type shows koilocytosis and other characteristic features of warty carcinoma in more than 10 % of the tumor mass, even in the intraepithelial variant (Fig. 13.33). Microscopically the presence of papillomatous tumor with long, rounded papillae showing fibrovascular cores and conspicuous koilocytosis is a very frequent finding (Fig. 13.34) and the papillary-warty variant typically overexpresses p16

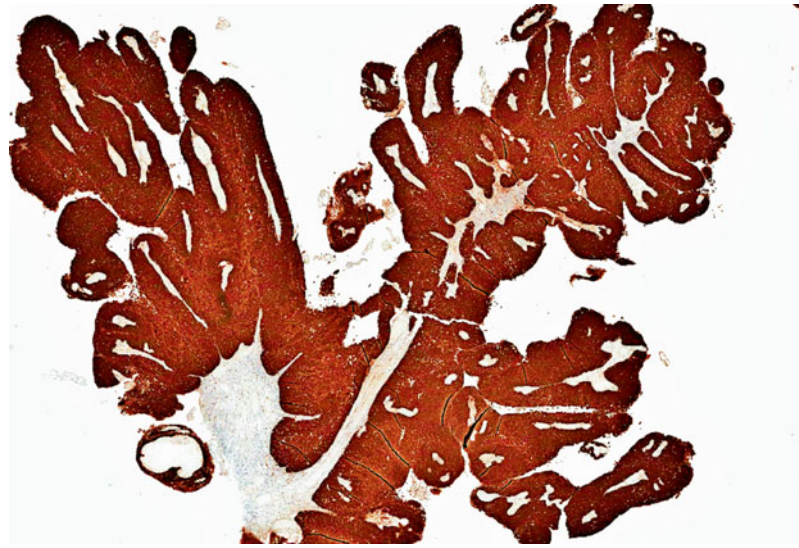

Fig. 13.35 p16 immunostaining in the papillary-warty variant. p16 immunostaining is diffusely positive in this PeIN with papillomatous growth

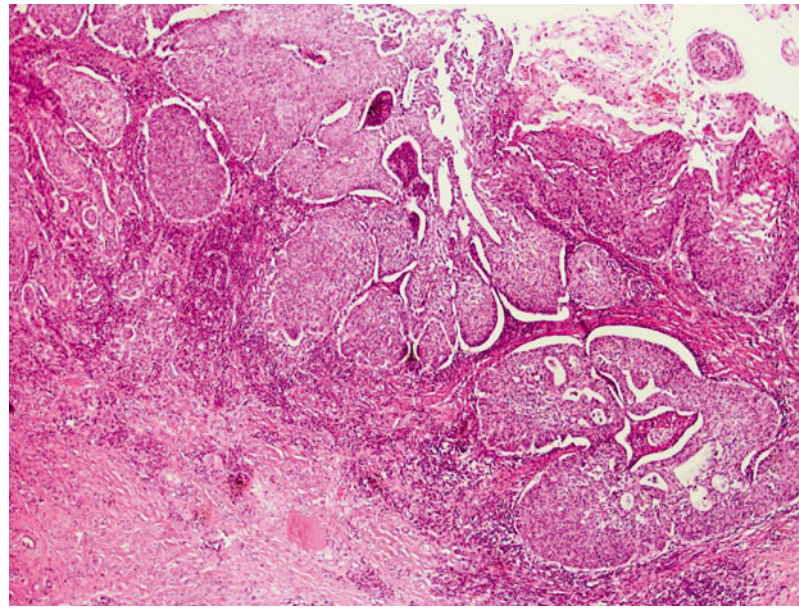

Fig. 13.36 Mixed carcinoma. Occurrence of pseudoglandular (acantholytic) carcinoma (on the right) adjacent to a well-differentiated SCC

(Fig. 13.35). Warty-basaloid carcinomas show a higher rate of metastasis (52 %) than warty carcinomas (33 %) [49], as the clinical behavior is related to the histologic grade, tumor thickness, and presence of vascular/perineural invasion (see Sect. "Prognostic Factors for SCC of the Penis"). Another classical example of mixed SCC is verrucous carcinoma with higher-grade foci consisting of usual SCC, so-called hybrid carcinoma [51]. Other less frequent combinations include usual-warty, mixed usual-basaloid, and occasionally observed cases of pseudoglandular carcinoma adjacent to a well-differentiated SCC (Fig. 13.36). Hybrid carcinoma occasionally presents lymph node metastases, which explains the presence of metastatic cases otherwise never reported in true verrucous carcinoma. The mortality rate is low and the selection of treatment

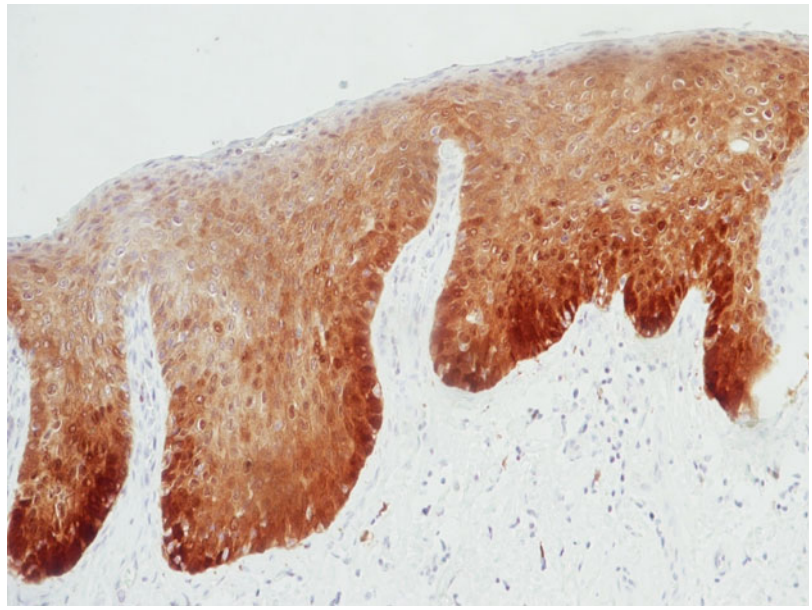

Fig. 13.37 p16 immunostaining in HPV-related (undifferentiated) penile intraepithelial neoplasia. Overexpression of p16 protein is associated with HPV

(conservative versus radical with or without groin dissection) requires careful histologic grading and assessment of perineural invasion [52].

Molecular Changes in Penile Carcinoma: Role of HPV Infection

The critical role of HPV infection in cancers of the lower genital tract has been delineated during the last several decades, and particularly the presence of high-risk HPV subtypes in a subset of around half of penile carcinomas is widely accepted [5].

The oncogenic role of HPV-16 in tumors of the mucosal epithelium of the glans has been reported in a review of human carcinogens [53]. HPV-16 infection appears to influence p16 protein and Rb gene expression, with the virus typically presenting in the nucleus of tumor cells in an episomal or integrated form. It is the most common viral type in penile carcinoma, accounting for 60–70 % of high-risk HPV-positive cancers [5, 43, 54]. Two mechanisms of dysregulated cell cycle control and apoptosis have been reported in penile carcinoma: one is HPV mediated and targets the $p16^{INK4a}$-cyclin D-Rb pathway [55], while the other is not HPV mediated, with p14 gene mutation, MDM amplification, and altered p53 expression (sometimes with mutation of the p53 gene). Both mechanisms bring about cell cycle arrest with altered apoptosis, while inactivation of the Rb gene results in loss of negative control of p16 with overexpression of p16 protein. The altered expression of p16 protein was first associated with HPV's oncogenic potential in cervical and genital lesions [24, 56].

Integrated HPV produces the E7 oncoprotein, which induces inactivation of the Rb gene and overexpression of the p16 protein, as can be detected by immunohistochemical staining (Fig. 13.37). In addition to p16 immunohistochemistry, the detection of HPV in clinical specimens is based on nucleic acid probe technology, using hybridization procedures (Southern blot, Northern blot, ISH, hybrid capture) and DNA/RNA detection by means of the more accurate and expensive real-time polymerase chain reaction (PCR). An HPV ISH reaction is the in situ detection of the integrated virus in the infected nucleus: a case is considered positive when unequivocal punctuated blue nuclear staining is observed in tumor cells (Fig. 13.38).

In a series of 48 penile carcinomas studied by tissue microarrays, Chaux et al. reported a combined methodology using p16 immunohistochemistry, routine morphology, and ISH [57].

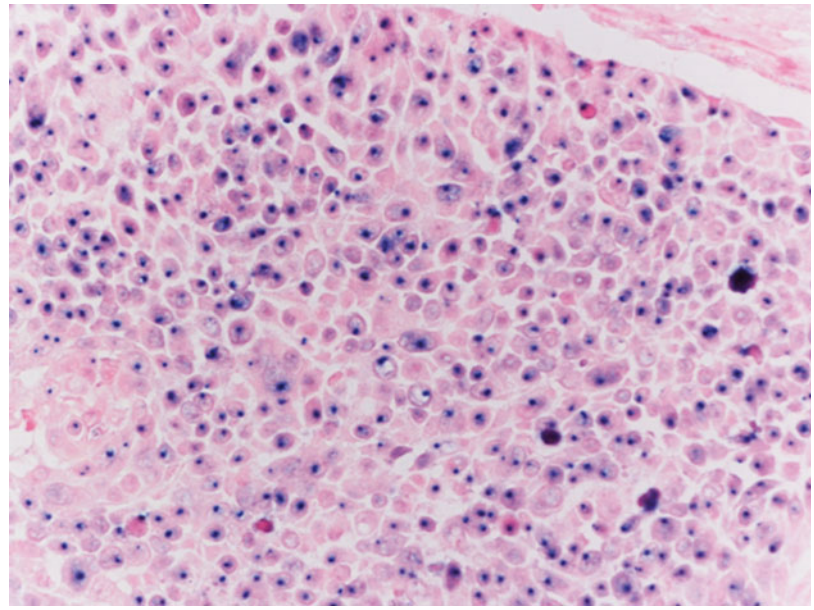

Fig. 13.38 Human papillomavirus ISH reaction. Blue nuclear staining is observed in tumor cells by chromogenic in situ hybridization (Courtesy of Dr A. Gloghini, Istituto Nazionale dei Tumori, Milan, Italy)

The gold standard technique was PCR, but according to the authors, the technical requirements and elevated costs preclude the routine use of PCR assays. They recommend combining the two techniques (p16 immunohistochemical staining and ISH) with routine morphology to enhance the sensitivity (88 % when this approach is applied) with sufficient specificity [57].

Alternative mechanisms targeting the $p^{16INK4a}$-cyclin D-Rb pathway have been investigated: the pathway can be disrupted by silencing the gene through promoter methylation and expression of the BMI-1 PcG gene, which has a critical downstream target involving $p16^{INK4a}$ and p14 [55].

The possible influence of HPV infection on the clinical outcome of penile cancer is debated. Some studies claim that the presence of high-risk HPV DNA in penile carcinoma predicts a favorable survival outcome [54], while other authors reported no survival differences [58]. Two studies showing the association of HPV infection and $p16^{INK4a}$ overexpression found overexpression of p16 to be associated with a favorable prognosis [59, 60], while in another recent tissue microarray study, the authors reported that neither HPV infection nor $p16^{INK4a}$ overexpression significantly predicted overall survival or cancer-specific survival [61]. A larger series of patients with long follow-up is required for the adequate definition of this prognostic factor.

Among the HPV-unrelated subtypes of SCC, verrucous carcinoma showed HPV DNA in 13 % of cases, while overexpression of p53 and Rb proteins was reported along with a low incidence of p16 expression in the large series studied by Stankiewicz [27]. This observation and the presence of altered expression of p21 and EGFR as well as AKT inactivation in HPV-positive and HPV-negative tumors have contributed to the dilemma that, although penile cancer arises by two separate mechanisms, one virus related and the other virus unrelated, there is a possible final common pathway to penile carcinogenesis.

One study investigated the human epidermal growth factor receptor (HER) family composed of the transmembrane tyrosine kinase receptors EGFR, HER2, HER3, and HER4 [62]. These receptors are activated by extracellular ligands stimulating intracellular signaling pathways, including the PI3K/AKT pathway, which regulate cell differentiation, migration, and survival. EGFR, HER3, and HER4 but not HER2 are associated with penile carcinogenesis. HPV-negative tumors tend to express significantly more phosphorylated EGFR (pEGFR) than HPV-positive tumors, and pEGFR expression correlates with activated AKT

protein, indicating that EGFR is an upstream regulator of AKT signaling in penile cancer. HER3 is inversely expressed, with significant overstaining in HPV-positive tumors, and its expression correlates positively with cytoplasmic AKT expression. HER4 and PTEN expression are not related to HPV infection. These molecular assessments have opened the way to targeted treatment with anti-EGFR agents. However, the results are still preliminary, and treated patients have been found to relapse after initial partial remissions [63].

Many other molecular markers have been investigated, but how high-risk HPV types impact on the expression of key cell cycle proteins such as p53, p21, p16, and others is far from being fully understood. Lam and Chan [64] analyzed the expression of p21 and p53 in 42 penile carcinomas and found p21 in 40 % of invasive cancers with an inverse relationship to p53. p53 immunostaining was found in all HPV-positive cases, but other authors reported an inverse or negative relation between these 2 factors, showing p53 expression in less differentiated tumors and in lymph node metastases, which would support the concept that p53 is a marker of worse prognosis [65]. Recent studies have demonstrated the implication of the PTEN/PI3K/AKT pathway in penile carcinogenesis [62, 66], but the suggested role of the mammalian target of rapamycin (mTOR) pathway in the development of lymph node metastasis deserves further investigation.

There have been few attempts to link chromosomal abnormalities to the biologic behavior of penile cancer. Genetic imbalances have been reported in penile cancer, and DNA sequence copy number gains were found in 8q24, 16p11-12, 20q11-13, 22q, 19q13, and 5p15 in one study [67]. Other candidate genes in the genomic map of penile cancer that might prove to be targets for rare metastatic cases include PRKCI, PI3K, DCUN1D1, LAMP3, and others associated with gains in 3p12.3 and S-phase kinase-associated protein 2, which is associated with gain and/or amplification of the 5p15.33–p11 region [68]. Although other cytogenetic changes have been described, none of these are characteristic. As with all malignant tumors, penile tumor progression involves the loss of cell-to-cell interaction and invasion of the extracellular matrix. A study by Campos et al. [69] showed that low expression of E-cadherin, an epithelial cell adhesion molecule, and increased immunoreactivity of the matrix metalloproteinases MMP-2 and MMP-9 were correlated with a higher risk of metastases; moreover, MMP-9 expression was an independent risk factor for recurrence.

As other genes are currently under investigation including COX-2, MYC, SOX2, and AT-rich interactive domain 1A (ARID1A), a clearer picture of the molecular changes in penile carcinomas is slowly emerging. The presence of a final common pathway to penile carcinogenesis with similar molecular mechanisms seems a possibility, although penile cancer arises by two separate mechanisms, one involving p53 and the other mediated by HPV in the subset of HPV-positive penile carcinomas.

Prognostic Factors for SCC of the Penis

The use of heterogeneous pathologic methodologies and the studies regarding variable patient populations without uniform treatment and follow-up have led to contradictory results and limitations in the pathologic evaluation of prognostic factors. In Table 13.3 the main prognostic factors for SCC of the penis are reported.

Table 13.3 Prognostic factors for squamous cell carcinoma of the penis. References in parentheses

Nodal status [70–74]
Histologic grade [75, 76]
Depth of infiltration [77]
Anatomical levels [78–80]
Perineural invasion [52]
Lymphatic [81] and vascular embolization [82]
Modality of growth, front pattern of invasion [1, 83]
Proliferative index [84]
Molecular factors [85]

Nodal Status

The single most important prognostic factor for overall outcome in penile carcinoma is the nodal status. Such is its importance that the 5-year and 10-year survival rates for patients with lymph node involvement are 48 % and 46 %, respectively, versus 91 and 88 % for patients with pathologically negative lymph nodes [80]. Prophylactic lymphadenectomy has a better 5-year survival rate than deferred lymphadenectomy, and indications for extended pelvic lymph node dissection are the number of metastatic inguinal lymph nodes, their maximum diameter, and the presence of extranodal spread [74]. Nomograms predictive of pathologic inguinal node involvement in patients with SCC have enough accuracy to evaluate the real incidence of metastases (on the basis of the clinical stage of the involved lymph nodes, grade, vascular invasion, and anatomical levels of invasion) [86] and to estimate predictions of survival at 5 years [87].

Histologic Grade

Histologic grade shows a highly accurate correlation with prognosis. A study in the Netherlands using the 3-tier grading system for SCC found in well-differentiated (grade 1) SCC 24 % of metastatic inguinal lymph nodes, compared with 46 % in moderately differentiated (grade 2) and 82 % in poorly differentiated (grade 3) SCC [75]. Any proportion of grade 3 SCC carries a poor prognosis [76].

Depth of Infiltration and Anatomical Levels of Invasion

The depth of infiltration has prognostic value and accurate measurement of tumor invasion in millimeters is required particularly in surgical specimens, both penectomy and circumcision, while the evaluation in small biopsies is generally unaccurate, given that only 9 % of biopsy results are confirmed in penectomies [17]. Measurement may be performed from the basement membrane to the deepest point of invasion [77]; the risk of metastases is especially high in tumors invading more than 10 mm and with infiltration of the corpora cavernosa in the glans or deep preputial dartos in the foreskin [78]. The invasion of anatomical levels is subject to error in pathology reports due to confusion of the anatomical location with the site of the tumor. The importance of this information is confirmed by the stage of penile cancer being based on the anatomical levels of invasion in the current TNM system [88] (Table 13.3). The anatomical levels of invasion, 1, 2, and 3, in the glans correspond to the lamina propria, corpus spongiosum, and corpora cavernosa, while levels 2 and 3 in the foreskin correspond to the dartos and skin [79]. They are evaluated with a scoring system referred to as "Prognostic Index" by Chaux et al. [80], which consists of the addition of numerical values given to histologic grade (1–3), deepest anatomical level involved by cancer (1–3), and presence of perineural invasion (0 or 1). According to the Prognostic Index, scores of 5 and 6 are associated with a high mortality rate [80].

Perineural Invasion, Lymphatic and Vascular Embolization

Perineural invasion is easily observed but it is not frequently reported in the diagnosis. It is an independent prognostic parameter associated with regional metastasis in tumors with 5–10 mm depth of invasion [52]. Lymphatic embolization and vascular embolization have been reported as independent predictive variables of inguinal lymph node involvement in patients with SCC of the penis according to a multicenter Italian study [82].

Modality of Growth, Front of Invasion, and Histologic Subtypes

The correlation between tumor growth pattern and presence of regional metastases and survival has been studied [1, 75]: high mortality was

found for patients having tumors with a vertical growth pattern (67 %), while the mortality dropped to 10 % in superficially spreading carcinomas [1]. Another factor affecting prognosis is the modality of growth of the deepest invasive tumor component in relation to the stroma: the infiltrative pattern of invasion was reported to be an independent risk factor for regional node metastasis [83].

According to their histologic subtype, penile carcinomas are subdivided into three risk groups for regional or systemic spread: verruciform tumors belong to the low-risk group, while about half of all penile cancers (including usual SCC and pleomorphic warty carcinomas) belong to the intermediate-risk group; the high-risk group comprises high-grade, deeply invasive tumors that are frequently metastatic at the onset, including basaloid, sarcomatoid, and adenosquamous carcinomas and poorly differentiated SCC.

Among the prognostic factors, histologic subtype was found to be less important than perineural invasion, histologic grade, and vascular invasion in multivariate analysis [18].

Proliferative Index and Molecular Prognostic Factors

Conflicting results have been reported in the literature about the relative risk of tumor metastasis according to different Ki67 values. Several recent series reported no correlation between proliferative index and survival, but two studies estimated a higher risk of lymph node metastasis in tumors with a high proportion of Ki67-positive tumor cells [89, 90].

Many different molecular prognostic factors have been investigated, but the enthusiasm for this research has dwindled because they lacked the levels of evidence for inclusion with a grade of recommendation in clinical practice guidelines [90, 91].

Among other factors, epithelial cadherin and MMP-9 [90], metastasis suppressor protein KAI1/CD82 [92], SOD2 [93], telomerase activity [94], squamous cell carcinoma antigen [95], cyclooxygenase expression (COX-1 and COX-2) [96], and genetic imbalances and ploidy status [97] have been investigated; they were reported to have different degrees of involvement in the pathogenesis of penile cancer and to be potential prognostic factors in this disease. Accumulation of p53 protein was found to be an independent predictor of lymph node metastases, with a significant correlation with poor outcome [54, 65].

Among oncologists dedicated to this pathology, the conviction is that "more research is needed to identify molecular markers which could lead to advances in personalized medicine" [91].

Local, Regional, and Systemic Spread

Local spread of the superficial spreading pattern of growth of penile cancers originating in the glans frequently shows extension to the coronal sulcus and foreskin, while foreskin carcinomas spread to the skin of the shaft, coronal sulcus, or glans. Similar growth features have been reported in intraepithelial pagetoid spread simulating Paget's disease [98]. The vertical growth pattern is associated with infiltration of anatomical levels and extension to the lamina propria, corpus spongiosum, albuginea, and corpora cavernosa. Extension to the penile fascia in cancer of the coronal sulcus involves deep penetration of the corpora cavernosa through the feeding vessels of the tunica albuginea, and rounded nodules of carcinoma ("satellite nodules") are sometimes observed separately from the main tumor mass in surgical samples. The importance of vascular (Fig. 13.39) and perineural invasion has been mentioned in the paragraph about prognostic factors.

Regional lymph node spread of penile cancer is common, while metastases to the pelvic nodes are less frequent and are mostly associated with inguinal lymph node involvement [74]. Anatomical variation of the sentinel lymph node, the first site of metastasis [99, 100], may interfere with the standardized protocol of lymph node dissection. Preoperative lymphoscintigraphy and dynamic sentinel node biopsy allow earlier detection of clinically negative metastatic lymph nodes, resulting in improved survival [70, 72, 73]. Systemic spread of penile cancer may involve the retroperitoneal nodes, periscrotal area, and subcutis of the abdomen (Fig. 13.40), heart, lung, bone, and liver.

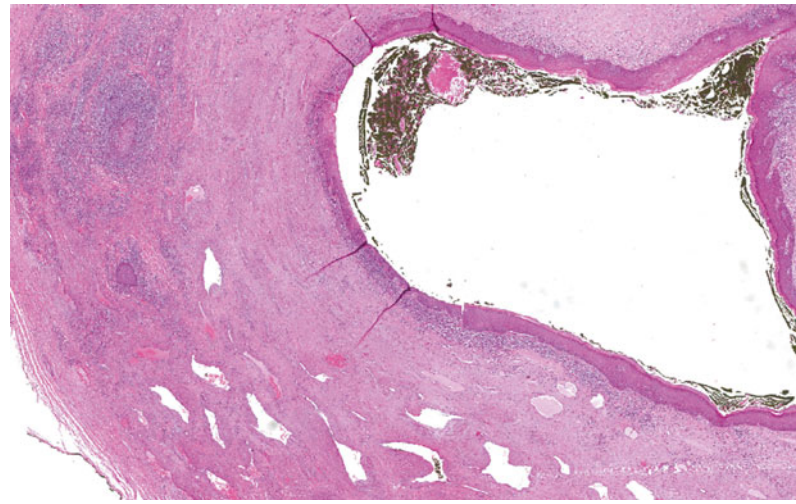

Fig. 13.39 Spread of penile cancer through the vessels of the urethral margin in a penectomy specimen

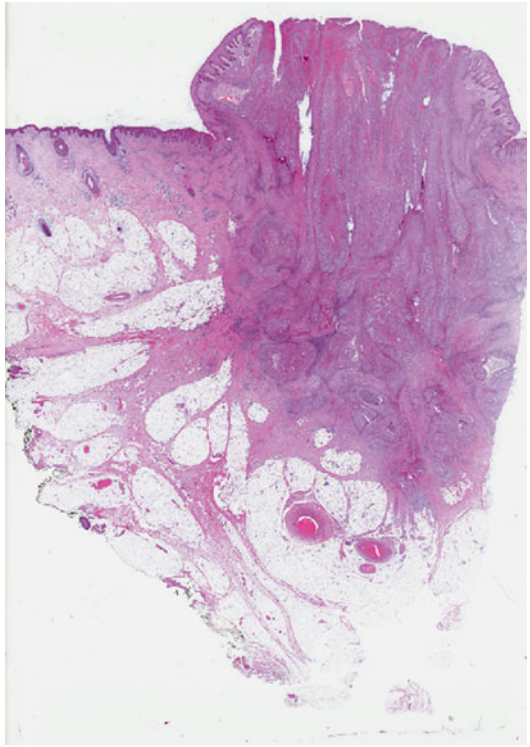

Fig. 13.40 Systemic spread of penile cancer. Squamous cell carcinoma located in the cutis of the abdomen

Positive Resection Margins and Recurrence

The prognosis of patients with recurrence after excision of penile carcinoma is dismal, with higher mortality in the subgroup of patients with recurrent tumors compared with the nonrecurrent subgroup [101]. This is the most important clinical consequence regarding the assessment of resection margins performed after penectomy or penile-preserving surgery [102]. It is still debated if local control can be obtained with margins measuring less than 10–15 mm in partial penectomies [103].

Accurate margin sampling in partial penectomies requires at least three sections: (1) urethra and periurethral tissue, (2) a section including both corpora cavernosa, and (3) the skin (foreskin or shaft with underlying dartos) [9]. In a series of 80 partial penectomies, 14 positive margins were observed [37]. Also other studies reported that local recurrences after limited surgical excision or partial penectomy are not uncommon [102]. Velazquez et al. reported involvement of the urethra and periurethral tissue including the penile fascia by carcinoma. They recommend frozen section examination of the urethral margin, which can be useful to detect tumor emboli within the lymphovascular spaces of the lamina propria and in the blood vessels of the periurethral corpus spongiosum [37]. Another common site of invasion of the glans is the coronal sulcus in cancers arising in the foreskin; a section of the sulcus has to be provided as margin. An uncommon site of positive resection margins is the corpus cavernosum, because of the barrier to tumor spread provided by the tunica albuginea. Leijte et al. analyzed the recurrence patterns in 700 patients from two referral centers for penile carcinoma

[104]. Patients receiving a penile-preserving procedure, those subjected to a wait-and-see policy for nodal status, and those with pN+ disease were at high risk of developing a recurrence, with an overall local recurrence rate after penile-preserving treatment of 27.7 %, of which 74.1 % occurring during the first 2 years [104].

Local recurrence increases the risk of regional inguinal and pelvic lymph node metastases [101]. Comparison of recurrent and nonrecurrent tumors showed that higher-grade tumors (i.e., basaloid and sarcomatoid) tended to be associated with recurrences, a finding that would dissuade clinicians from performing partial penectomies or local excisions in these aggressive variants [101].

Staging

The TNM classification of carcinomas of the penis is reported in Table 13.4. The classification is based on anatomical levels [79, 80], but it is known that the risk of metastases increases in tumors infiltrating more than 5 mm and is high when the corpora cavernosa in the glans and the dermis in the foreskin are affected. Further studies need to evaluate substaging of stage T2 to differentiate between superficial and deep corpus spongiosum infiltration and to take into account carcinomas of the penis limited to the foreskin, which are absent from the latest TNM classification.

Table 13.4 TNM staging system for penile carcinomas (UICC [88])

Primary tumor (T)
Tx primary tumor cannot be assessed
T0 no evidence of primary tumor
Tis carcinoma in situ; *Ta* noninvasive verrucous carcinoma
T1a tumor invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated; *T1b* tumor invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated
T2 tumor invades corpus spongiosum or cavernosum
T3 tumor invades urethra
T4 tumor invades other adjacent structures (perineum, scrotum, prostate)
Regional lymph nodes (*N*)
N0 no regional lymph node metastasis
N1 metastasis in a single inguinal lymph node
N2 metastasis in multiple or bilateral inguinal lymph nodes
N3 extranodal extension of lymph node metastasis or metastasis in pelvic lymph nodes (unilateral or bilateral)
Distant metastasis (*M*)
M0 no distant metastasis
M1 distant metastasis

Other Tumors

Clear-Cell Carcinoma

The unusual clear-cell histologic type is a cancer occurring in the foreskin as a proliferation with prominent clear-cell changes and sometimes extensive necrosis. A few cases have been reported showing periodic acid-Schiff positivity as well as MUC1 and EMA immunostaining of the clear cells [105]. The clear-cell changes resemble the histologic features of renal cell carcinoma and are focally observed in some warty carcinomas of the penis. Clear-cell carcinoma is an HPV-related tumor with aggressive behavior which warrants radical treatment, i.e., total penectomy with groin dissection.

Giant Condyloma

This tumor, sometimes referred to as Buschke-Löwenstein tumor, is described in Chap. 12.

Paget's Disease

Primary Paget's disease is an intraepithelial growth of uncertain origin, sometimes originating from the apocrine ducts or sweat glands in the foreskin. It is characterized by basally located large atypical cells with abundant mucin-rich cytoplasm (Fig. 13.41).

Secondary Paget's disease is pagetoid intraepithelial spread of typical penile SCC [98] or – less frequently – of bladder or urethral carcinoma. This extension of adjacent tumors tends to affect the glans in the perimeatal region, extending to the perineum and scrotum.

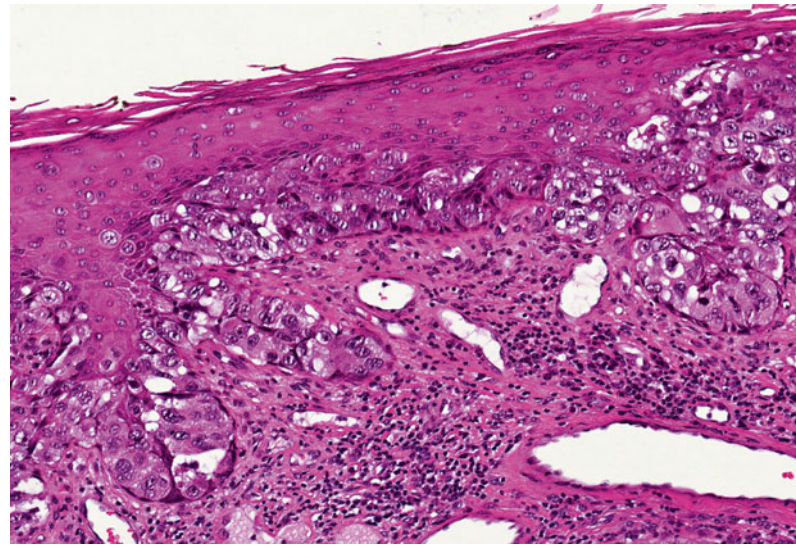

Fig. 13.41 Paget's disease. Large round atypical Paget's cells in the epithelium of the glans

Table 13.5 Immunohistochemistry of Paget's disease

Antibody	Paget's disease	Squamous cell CIS	Melanoma in situ	Urothelial carcinoma
CEA	+	–	–	–
CK7	+	–	–	+
CK20	–	–	–	+
GCDFP-15	+	–	–	–
S100	–	–	+	–
p63	±	+	–	+

Partially reported in Lopez-Beltran [106]

The immunohistochemical findings are quite peculiar: in Table 13.5 the immunostainings of extramammary Paget's disease and different penile tumors are presented.

Among these entities the most common is pagetoid urothelial carcinoma of the penis, where CK20 in addition to CK7 and p63 are useful immunohistochemical markers [107, 108]. A less frequent and less problematic lesion is clear-cell papulosis of the foreskin [109].

Melanoma of the Penis

Since the first description in the mid-nineteenth century, fewer than 100 cases of penile melanoma have been reported, accounting for approximately 1.4 % of all primary penile tumors [110]. Primary melanomas are mainly localized in the glans (Fig. 13.42) and have similar behavior to cutaneous melanoma, with comparable tumor thickness [111]. The adverse prognostic factors these tumors have in common are ulceration, tumor depth of 3.5 mm or more, and tumor diameter of >15 mm. The presence of lymph node metastasis at presentation carries a poor prognosis. Sometimes the presence of an in situ component may complicate the differential diagnosis with Paget's disease (Fig. 13.43). In such cases the expression of melanocytic markers (S100 protein, HMB45 protein, melan-A) can be helpful. A common presentation is mucous lentiginous melanoma, characterized by the proliferation of atypical melanocytes in the basal layer of the epidermis and by lengthening of the rete ridges as often seen in lentiginous tumors [112] (Fig. 13.44). Clinically it is easy to differentiate from penile melanosis, which is characterized by large pigmented macules affecting the glans and foreskin, and at the microscopic level by basal cell hyperpigmentation, stromal melanophages, and melanocytic hyperpla-

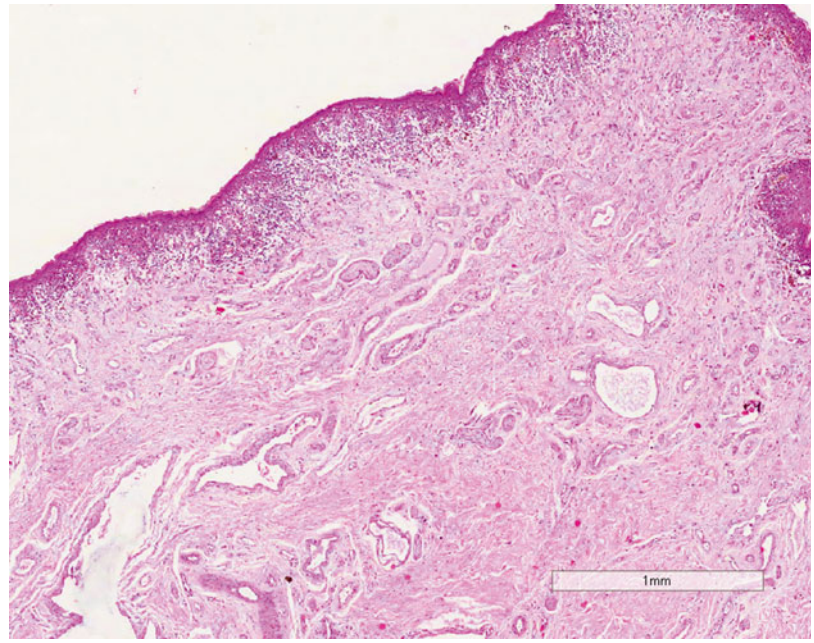

Fig. 13.42 Melanoma of the glans. Common presentation of melanoma in the glans as mucous lentiginous melanoma with marked inflammatory reaction in the dermis

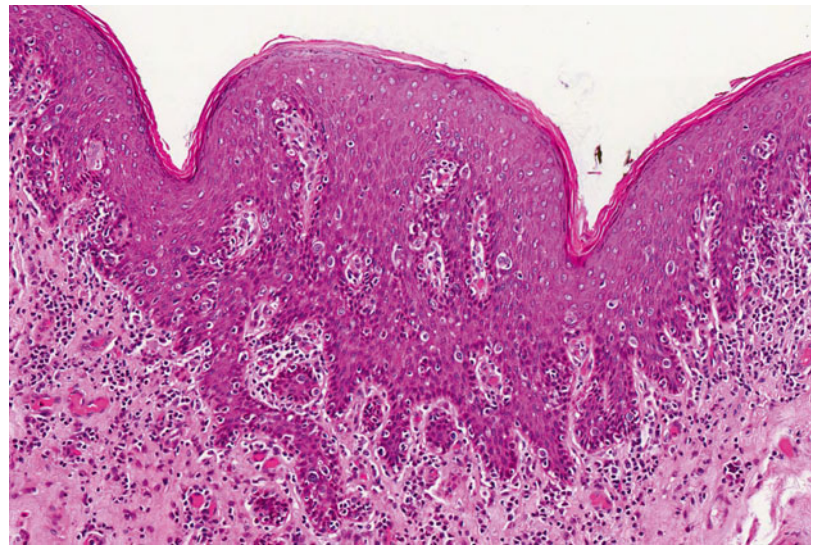

Fig. 13.43 Melanoma in situ. The presence of single, small nests of melanoma cells in the superficial layers of the glandular epithelium provides compelling evidence for in situ melanoma (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

sia [113]. The absence of cytologic atypia is a distinctive feature of this benign condition.

Soft Tissue Tumors

The most common sarcomas of the penis are those of vascular origin, including benign variants such as hemangioma, epithelioid hemangioma, angiokeratoma, and lymphangioma as well as malignant variants such as angiosarcoma, epithelioid hemangioendothelioma, and Kaposi sarcoma. Malignant tumors of myoid, fibrous, and neural etiology have also been described. It is particularly important for surgical pathologists, who rarely encounter these tumors, to distinguish sarcomas from sarcomatoid carcinomas [114].

Benign Soft Tissue Tumors

The majority of benign mesenchymal penile neoplasms including hemangiomas, lymphangiomas,

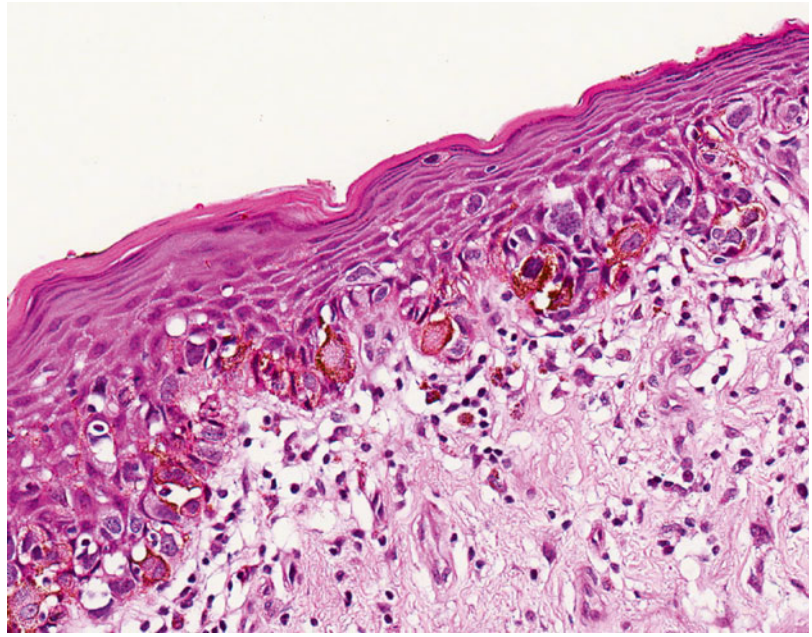

Fig. 13.44 Mucous lentiginous malignant melanoma of the penis. Basilar proliferation of atypical melanocytes in the basal layer

and epithelioid hemangiomas have been reported in case reports; the latter tumors are sometimes confused with epithelioid hemangioendothelioma or epithelioid angiosarcoma [115]. Other less common tumors are neurofibromas, schwannomas, granular cell tumors, leiomyomas, glomus tumors, dermatofibromas, myofibromas, and juvenile xanthogranulomas. Less commonly reported types are lipoma, angiolipoma, and nodular fasciitis [114]. Myointimoma is an unusual but distinct vascular benign tumor affecting the corpus spongiosum and originating from the vascular intima in young adults [116]. Microscopically the lesion is a myointimal intravascular plexiform lesion showing uniform myoid cells with minimal atypia [116, 117]. It can be managed with conservative surgery.

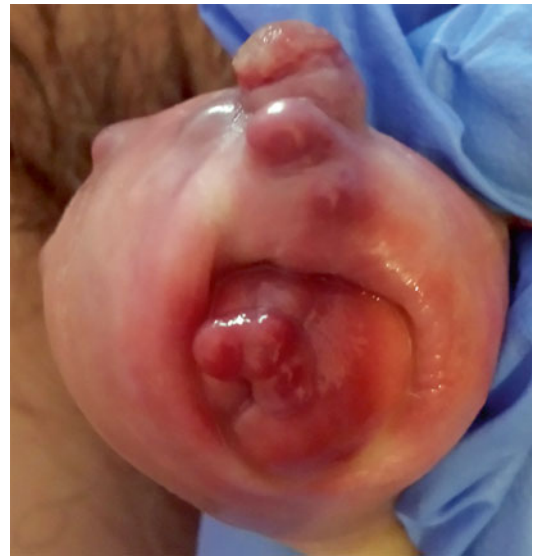

Fig. 13.45 Kaposi sarcoma. Multiple reddish nodules in the glans and foreskin of the penis (Courtesy of Dr T. Torelli, Istituto Nazionale dei Tumori, Milan, Italy. Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

Malignant Soft Tissue Tumors

Kaposi sarcoma is by far the most common malignant soft tissue tumor affecting the penis [9]. It exists in several different clinical subtypes, all displaying similar microscopic features. Kaposi sarcoma in young adults affects individuals with underlying immunodeficiency caused by HIV infection, immunosuppressive or chemotherapeutic medication, lymphomas, or inherited syndromes. The most common location is the glans, where Kaposi sarcoma presents as purple papules or nodules (Fig. 13.45), which, in well-established lesions, show extravasated erythrocytes, vessels encircling vessels, and the characteristic spindle cell proliferation admixed

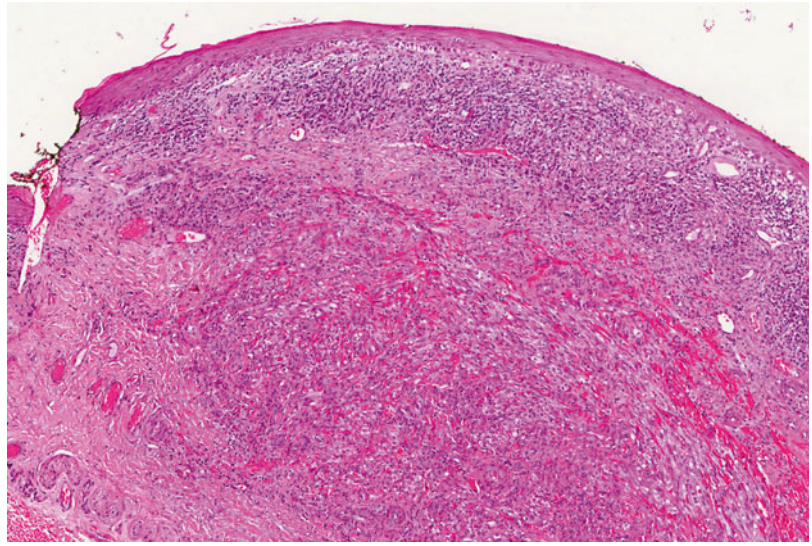

Fig. 13.46 Kaposi sarcoma. Microscopic appearance of the case of Fig. 13.45 showing multiple nodules of Kaposi sarcoma with spindle cell proliferation admixed with slit-like vessels

with slit-like vessels (Fig. 13.46). Tumor cells show nuclear positivity for human herpes virus 8 (HHV-8) staining, which is confirmative of the diagnosis [118, 119].

Leiomyosarcoma

Leiomyosarcoma of the penis is a very rare disease of mid and late adult life [120], arising from both superficial and deep smooth muscle elements. All deep-seated tumors are presumed to be of vascular (corpus cavernosum and corpus spongiosum) origin, while the superficial tumors occur as circumscribed nodules probably derived from the superficial vasculature of the penis or as infiltrative lesions probably derived from the dartos [121].

The most accurate predictors of outcome are tumor depth [122] and size, but only well-demarcated deep-seated tumors require partial or total penectomy, while superficial leiomyosarcomas can be treated with conservative surgery. All tumors contain smooth muscle cells with blunt-ended sometimes pleomorphic nuclei that form fascicles. Tumor growth pattern, mitotic count, and grading are the distinguishing microscopic features. The main differential diagnoses are leiomyoma, myointimoma, nodular Kaposi sarcoma, malignant fibrous histiocytoma, and sarcomatoid carcinoma. Kaposi sarcoma is more frequent than leiomyosarcoma (2:1), and its diagnostic clues (see paragraph on Kaposi sarcoma) in superficial lesions can resemble the fascicular architecture of leiomyosarcoma. Strong reactivity for CD34 and CD31 and the absence of desmin and factor VIII immunostains distinguish nodular Kaposi sarcoma from leiomyosarcoma, which shows alpha muscle actin-positive and HHF35-positive immunostains as well.

Epithelioid Sarcoma

This highly unusual entity occurs either as single or multiple superficial penile nodules or urethral stenosis, symptoms that epithelioid sarcoma shares with Peyronie's disease [123]. Progressive growth should suggest a malignancy and warrant biopsy, because epithelioid sarcoma requires prompt and aggressive intervention. Histologically, epithelioid sarcoma is characterized by spindle and epithelioid cells with eosinophilic cytoplasm, often surrounding an area of central necrosis with a pseudogranulomatous appearance. The epithelioid cells have moderate atypia with vesicular nuclei and prominent nucleoli [124] (Fig. 13.47).

Positive immunostaining for vimentin, EMA, CD99, and CD34 (in 70 % of cases) allows the differential diagnosis with other soft tissue tumors

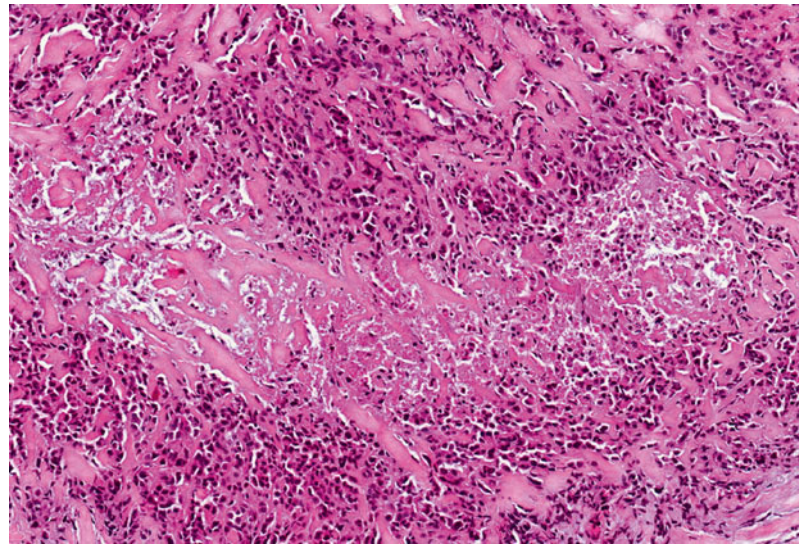

Fig. 13.47 Epithelioid sarcoma. Epithelioid cells with eosinophilic cytoplasm surrounding an area of necrosis

Table 13.6 Typical immunohistochemical staining profile of soft tissue tumors

Neoplasm	Typical immunohistochemical staining profile
Sarcomatoid squamous cell carcinoma	
Sarcomatoid urothelial carcinoma	AE1/AE3 +, EMA +, vimentin +, p53 *variable*, actin -, desmin -, S100 -, CD34 -
Leiomyosarcoma	Desmin +, MSA (HHF35) +, may show keratin *focal*, EMA *focal*, CD34 *focal*, S100 *focal*
Kaposi sarcoma	CD31 +, CD34 +, HHV-8 +, factor VIII -, desmin -
Spindle cell melanoma	S100 +, HMB45 +, melan-A/MART-1 +, microphthalmia transcription factor +, tyrosinase +
Desmoplastic melanoma	S100 +, MSA (HHF35) + (58 % of cases), HMB45 -, melan-A/MART-1 -, microphthalmia transcription factor -, tyrosinase -, may show NSE +, EMA +, NKI/C-3 +, alpha-SMA +
Dermatofibrosarcoma protuberans	CD34 +, factor XIIIa -, t(17;22) by FISH
Rhabdomyosarcoma	Myogenin +, desmin +, MSA (HHF35) +, t(2;13), or t(1;13) in alveolar variant
Myointimoma (not typically a spindle cell neoplasm)	MSA (HHF35) +, alpha-SMA +, calponin +, desmin *minimal reactivity*

(see Table 13.6). A case of pediatric epithelioid sarcoma has been reported [125]. Most recurrences and metastases develop within 3 years of treatment, but late metastases may occur.

Lymphomas

Lymphomas are very infrequently observed as primary penile tumors or secondary localizations of systemic disease. Histiocytic tumors are rare. Priapism has been reported secondary to leukemia in a highly uncommon case [126]. When penile lymphomas do occur, they are mostly non-Hodgkin B-cell lymphomas of the diffuse large-cell type (Fig. 13.48), although other infrequent subtypes may occur including mucosa-associated lymphoid tissue (MALT) lymphoma and T-cell, anaplastic large-cell, and CD30-positive lymphomas. Chemotherapy is generally effective [127].

Metastatic Tumors of the Penis

Metastases to the penis from any kind of tumor are rare. The most common sites of origin are the urinary bladder and prostate, followed by the kidney, gastrointestinal tract, and testis

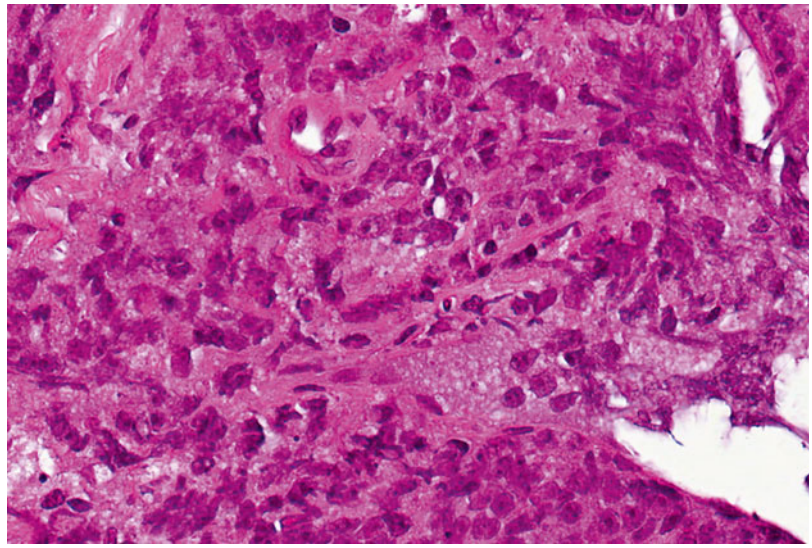

Fig. 13.48 B-cell non-Hodgkin lymphoma. Biopsy of the glans with artifacts showing diffuse large B-cell-type non-Hodgkin lymphoma

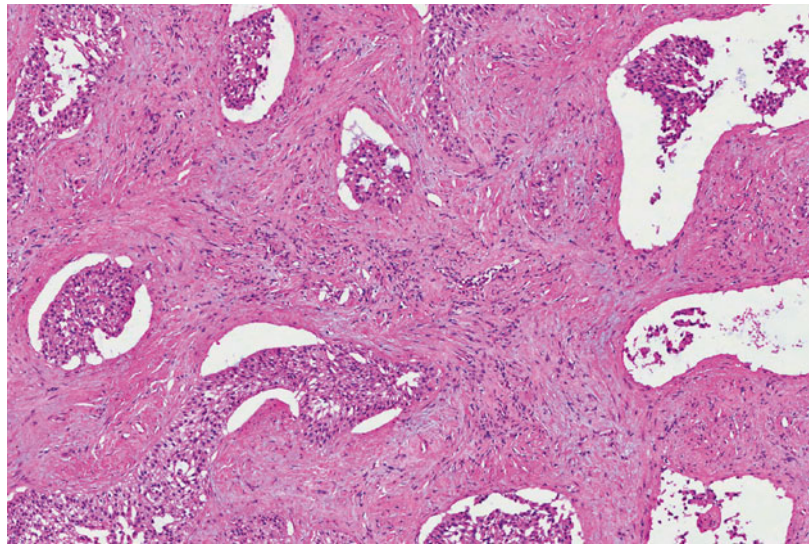

Fig. 13.49 Urothelial carcinoma metastatic to the glans. Angioinvasion in the corpus cavernosum with urothelial aggregates from a metastatic bladder carcinoma

(seminomatous germ cell tumors as well as embryonal carcinomas). Nonpelvic organs have been less frequently reported as primary sites, e.g., the lung, stomach, and pancreas [128, 129]. Commonly the metastasis occurs in the corpus cavernosum of the shaft [129]. Presentation with multiple palpable nodules is frequent, but in almost half of the cases, a prominent clinical finding is priapism ("malignant priapism") [130]. A frequent observation is extension to the glans of urethral urothelial carcinoma (Fig. 13.49).

Tumorlike Lesions

Peyronie's Disease

Peyronie's disease is characterized by a fibrous plaque or scar within the tunica albuginea of the penile shaft, producing an abnormal curvature of the penis [131]. Its pathogenesis appears to be multifactorial, but from a histologic point of view, Peyronie's disease seems strictly related to superficial fibromatosis [9] and persistent chronic inflammation, probably as a result of repetitive stress

microtrauma to the penis [132], urethral instrumentation, hypertension, and other factors [9]. The hallmark of the disease, that is to say the fibrous plaque, involves fibroblasts and myofibroblasts, but frequently the lesion is sclerotic with hypocellular areas and in rare cases calcification or ossification admixed with some inflammatory cells. Increased levels of transforming growth factor β1 seem to play a role in the development of the fibrotic plaques [133]. Treatment is mainly surgical, but rare spontaneous regression has been reported.

Lichen Sclerosus et Atrophicus

See Chap. 12.

Melanosis (Lentiginosis)

Melanosis is characterized by large pigmented macules, often multifocal and with irregular borders, affecting the glans and foreskin. Histology shows basal layer hyperpigmentation, epithelial and melanocytic hyperplasia, and stromal melanophages. The lesion has the potential to enlarge, and the absence of melanocytic atypia is a hallmark of this benign condition [113].

Frozen Section

The main indications for frozen sections in penile cancer are examination of the surgical margins and assessment of the nodal status; microscopic tumor is present in 5–30 % of partial penectomies, and frozen section examination of resection margins can lead to a reduction of the incidence of positive surgical margins and recurrence in SCC [103]. Intraoperative examination of the surgical margins includes the skin, corpora cavernosa, corpus spongiosum, urethra, and periurethral tissue. In the majority of surgical margins examined during partial or total penectomies, shaved margins are taken [134].

The most frequent sites of involvement by carcinoma are the periurethral corpus spongiosum, lamina propria, and urethra. Frozen sections are not commonly done in total penectomies, but in superficial spreading carcinoma, possible extension to the skin of the shaft requires surgical margin evaluation. The use of frozen section examination for sentinel lymph node biopsies is controversial [135]. Clinical examination and imaging techniques remain inaccurate for detecting micrometastases. In some centers frozen section is performed in sentinel node biopsy for patients with poorly differentiated, high-grade SCC [134]. Cytologic imprint preparation could be useful to detect metastases [136]. Other details about the pathological assessment of frozen section examination in penile specimens are reported in Chap. 14.

Malignant Lesions of the Scrotum

Squamous Cell Carcinoma

Improved hygiene conditions have led to a marked decrease in the incidence of scrotal carcinoma [9]. This tumor is linked to numerous occupational carcinogens, but nowadays the incidence is 5–10 cases per 10 million population in the USA [9]. The historical importance of occupational carcinogens is exemplified by Percivall Pott's investigation into the incidence of scrotal carcinoma in chimney sweeps, as mentioned in the 2011 Pulitzer Prize winning book by Siddhartha Mukherjee [137]. Most scrotal carcinomas are well to moderately differentiated keratinizing SCCs. SCC of the scrotum is considered and staged as skin carcinoma [9]. Unusual variants (basaloid, papillary, verrucous) are exceptional occurrences in this rare tumor. The presence of dysplastic changes in the epithelium adjacent to the tumor and possible analogies with precancerous conditions of the penis suggest that the HPV-related variant and differentiated squamous intraepithelial lesions have an analogous appearance to penile precursor lesions [11].

Extramammary Paget's Disease

The male genitalia were the first extramammary site described by Crocker as the site of Paget's disease [138]. It is a very unusual neoplasm with

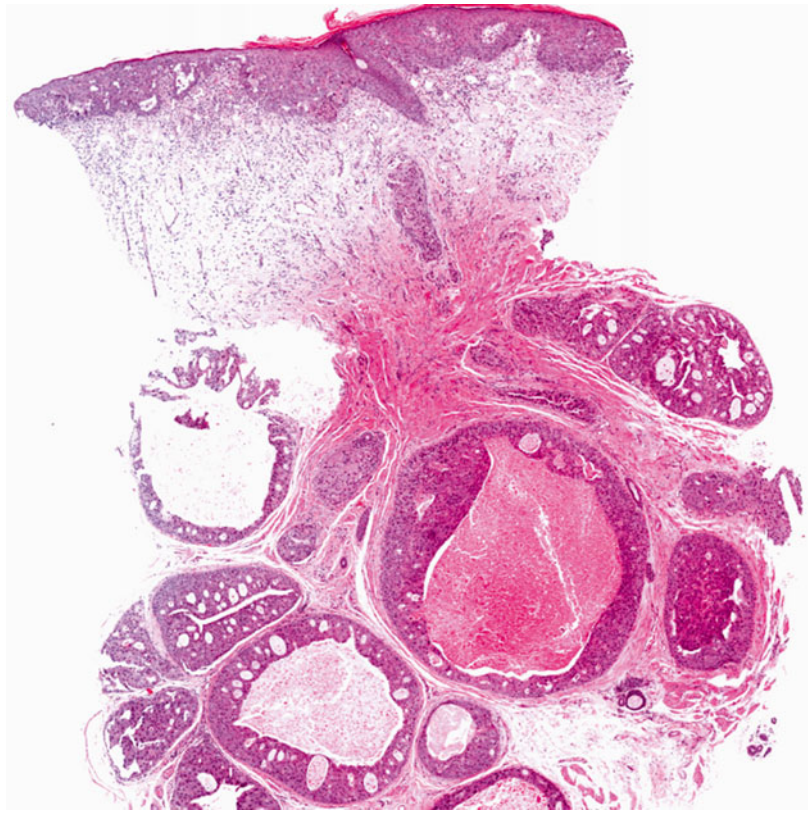

Fig. 13.50 Paget's disease of the scrotum. The epidermis of the scrotum colonized by a population of large, round, or oval atypical cells (Paget's cells) with clear cytoplasm and vesicular nuclei; there are gland-like neoplastic foci with the appearance of tubular glands in the reticular dermis (Published with kind permission of ©Maurizio Colecchia 2015. All Rights Reserved)

fewer than 30 cases reported at the beginning of this century [139].

On physical examination scrotal Paget's disease manifests as an erythematous, eczematoid lesion that is difficult to distinguish from Bowen's disease or in situ carcinoma. Pathognomonic Paget's cells (atypical large, clear, round cells) are observed with intraepidermal localization, rarely involving the dermis. This tumor is presumed to be an intraepidermal adenocarcinoma. Like mammary Paget's disease, scrotal lesions may be the result of epidermotropic spread from an underlying adnexal malignancy (Fig. 13.50) [140], also when secondary involvement of acrosyringeal structures can be observed. Other uncommon sites of extraepidermal origin are the colon-rectum and the urogenital tract [9]. Immunohistochemical findings include the expression of CEA, low-molecular-weight cytokeratins (CK7), CAM 5.2, EMA (Fig. 13.51), mucicarmine, MUC1, and gross cystic disease fluid protein 15 (GCDFP-15) [108]. Local excision may be useful with intraoperative examination of the margins. When radical surgery is difficult to accomplish due to the size of the lesion, topical chemotherapy followed by wide excision and a reconstructive procedure is the treatment of choice.

Basal Cell Carcinoma

Fewer than 50 cases of scrotal BCC have been reported to date [141], even if in terms of incidence it is the third most common malignant scrotal tumor. The differential diagnosis with basaloid SCC is important because of the dismal prognosis of the latter. While scrotal BCC shows the same histopathologic features as its nongenital cutaneous counterpart, it appears to be more aggressive.

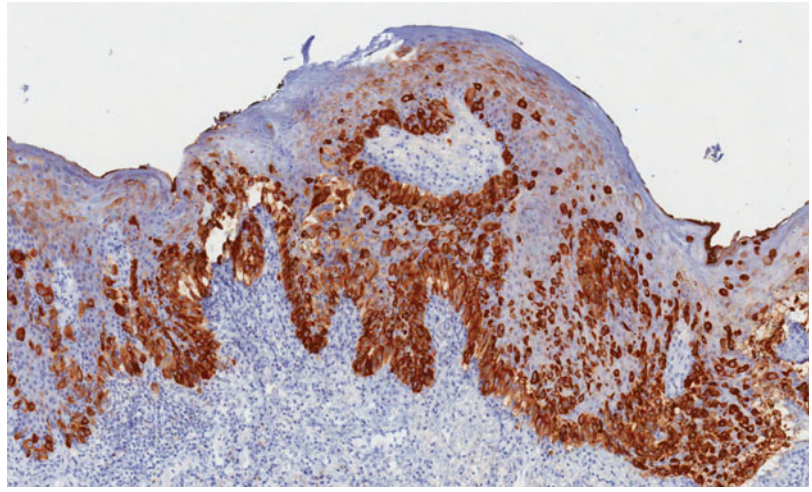

Fig. 13.51 EMA immunostaining in Paget's disease of the scrotum. Immunohistochemical stain of Paget's disease of the scrotum reported in Fig. 13.50 shows diffuse reactivity with epithelial membrane antigen (EMA)

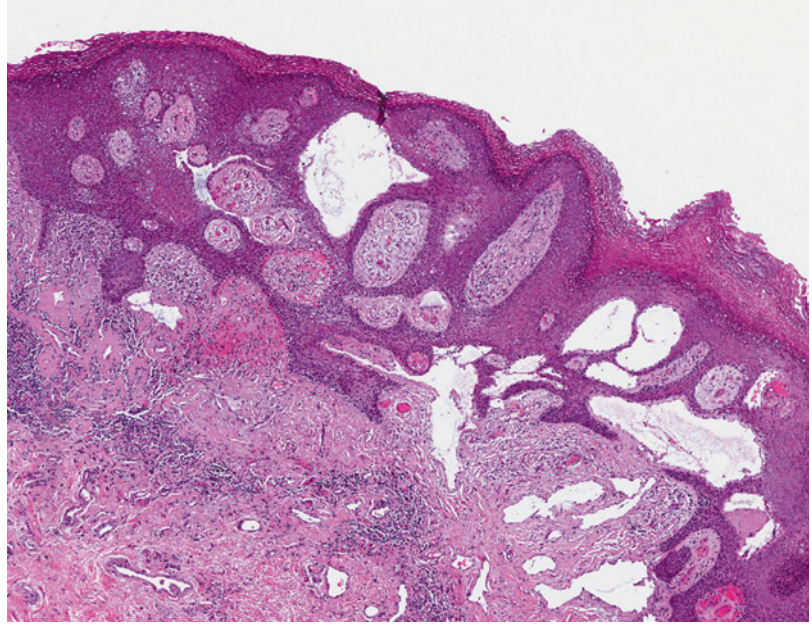

Fig. 13.52 Lymphangioma. Scrotal lymphangioma occurring with scrotal discomfort: the empty spaces devoid of blood have delicate valves. A thin smooth muscle wall is present

Other Lesions

Anecdotal examples of other benign and malignant lesions of the scrotum have been reported mostly as case reports. They included hemangiomas, lymphangiomas (Fig. 13.52), lipomas, granular cell tumors, schwannomas, solitary fibrous tumors, angiomyxomas, and very rare scrotal sarcomas (leiomyosarcoma, liposarcoma, epithelioid sarcoma, rhabdomyosarcoma) [142]. Tumor histology is one of the most important independent prognostic factors [143].

References

1. 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;9:111–20.
2. Chaux A, Lezcano C, Cubilla AL, Tamboli P, Ro J, Ayala A. Comparison of subtypes of penile squamous cell carcinoma from high and low incidence geographical regions. Int J Surg Pathol. 2010;18:268–77.
3. Chaux A, Velazquez EF, Amin A, Soskin A, Pfannl R, Rodríguez IM, Barreto JE, Lezcano C, Ayala G,

Netto GJ, Cubilla AL. Distribution and characterization of subtypes of penile intraepithelial neoplasia and their association with invasive carcinomas: a pathological study of 139 lesions in 121 patients. Hum Pathol. 2012;43:1020–7.
4. Gregoire L, Cubilla AL, Reuter VE, Haas GP, Lancaster WD. Preferential association of human papillomavirus with high-grade histologic variants of penile-invasive squamous cell carcinoma. J Natl Cancer Inst. 1995;87:1705–9.
5. Miralles-Guri C, Bruni L, Cubilla AL, Castellsagué X, Bosch FX, de Sanjosé S. Human papillomavirus prevalence and type distribution in penile carcinoma. J Clin Pathol. 2009;62:870–8.
6. Mentrikoski MJ, Stelow EB, Culp S, Frierson Jr HF, Cathro HP. Histologic and immunohistochemical assessment of penile carcinomas in a North American population. Am J Surg Pathol. 2014;38:1340–8.
7. Chaux A, Cubilla AL. The role of human papillomavirus infection in the pathogenesis of penile squamous cell carcinomas. Semin Diagn Pathol. 2012;29:67–71.
8. Chaux A, Velazquez EF, Algaba F, Ayala G, Cubilla AL. Developments in the pathology of penile squamous cell carcinomas. Urology. 2010;76:S7–14.
9. Epstein JH, Cubilla AL, Humphrey PA. Tumors of the prostate gland, seminal vesicles, penis and scrotum. Washington, DC: American Registry of Pathology AFIP Atlas of tumor pathology 3rd series, 2011. Fascicle 14, p. 405–612.
10. Longpre MJ, Lange PH, Kwon JS, Black PC. Penile carcinoma: lessons learned from vulvar carcinoma. J Urol. 2013;189:17–24.
11. Velazquez EF, Amin MB, Cubilla AL. Penis and scrotum. Chapter 14. In: Amin MB, Eble JN, Grignon DJ, Srigley JR, editors. Urologic pathology. Philadelphia: Lippincott Williams and Wilkins; 2014.
12. Velazquez EF, Cubilla AL. Lichen sclerosus in 68 patients with squamous cell carcinoma of the penis: frequent atypias and correlation with special carcinoma variants suggests a precancerous role. Am J Surg Pathol. 2003;27:1448–53.
13. Oertell J, Duarte S, Ayala J, Chaux A, Velazquez EF, Cubilla AL. Squamous cell carcinoma (SCC) exclusive of the foreskin: distinctive association with low grade variants, multicentricity and lichen sclerosus. Mod Pathol. 2002;15:175A.
14. Fukunaga M, Yokoi K, Miyazawa Y, Harada T, Ushigome S. Penile verrucous carcinoma with anaplastic transformation following radiotherapy. A case report with human papillomavirus typing and flow cytometric DNA studies. Am J Surg Pathol. 1994;18:501–5.
15. Sanchez DF, Canete S, Fernandez-Nestosa MJ, Lezcano C, Rodriguez I, Barreto J, Alvarado-Cabreo I, Cubilla AL. HPV- and non-HPV-related subtypes of penile squamous cell carcinoma (SCC): morphological features and differential diagnosis according to the new WHO classification (2015). Semin Diagn Pathol. 2015;32:198–221.
16. Chaux A, Velazquez EF, Barreto JE, Ayala E, Cubilla AL. New pathologic entities in penile carcinomas: an update of the 2004 World Health Organization classification. Semin Diagn Pathol. 2012;29:59–66.
17. Velazquez EF, Barreto JE, Rodriguez I, Piris A, Cubilla AL. Limitations in the interpretation of biopsies in patients with penile squamous cell carcinoma. Int J Surg Pathol. 2004;12:139–46.
18. Guimarães GC, Cunha IW, Soares FA, Lopes A, Torres J, Chaux A, Velazquez EF, Ayala G, Cubilla AL. Penile squamous cell carcinoma clinicopathological features, nodal metastasis and outcome in 333 cases. J Urol. 2009;182:528–34.
19. Kurman RJ, Toki T, Schiffman MH. Basaloid and warty carcinomas of the vulva. Distinctive types of squamous cell carcinoma frequently associated with human papillomaviruses. Am J Surg Pathol. 1993;17:133–45.
20. Davies SW. Giant condyloma acuminata: incidence among cases diagnosed as carcinoma of the penis. J Clin Pathol. 1965;18:142–9.
21. Cubilla AL, Velazques EF, Reuter VE, Oliva E, Mihm Jr MC, Young RH. Warty (condylomatous) squamous cell carcinoma of the penis: a report of 11 cases and proposed classification of 'verruciform' penile tumors. Am J Surg Pathol. 2000;24:505–12.
22. Epstein JI, Netto GJ. Differential diagnosis in surgical pathology: genitourinary system. Chapter 5: penis/scrotum. Philadelphia: Lippincott Williams and Wilkins; 2014.
23. Bezerra AL, Lopes A, Landman G, Alencar GN, Torloni H, Villa LL. Clinicopathologic features and human papillomavirus dna prevalence of warty and squamous cell carcinoma of the penis. Am J Surg Pathol. 2001;25:673–8.
24. Cubilla AL, Lloveras B, Alejo M, Clavero O, Chaux A, Kasamatsu E, Monfulleda N, Tous S, Alemany L, Klaustermeier J, Muñoz N, Quint W, de Sanjose S, Bosch FX. Value of p16(INK)^4(a) in the pathology of invasive penile squamous cell carcinomas: A report of 202 cases. Am J Surg Pathol. 2011;35:253–61.
25. Chan KW, Lam KY, Chan AC, Lau P, Srivastava G. Prevalence of human papillomavirus types 16 and 18 in penile carcinoma: a study of 41 cases using PCR. J Clin Pathol. 1994;47:823–6.
26. Johnson DE, Lo RK, Srigley J, Ayala AG. Verrucous carcinoma of the penis. J Urol. 1985;133:216–8.
27. Stankiewicz E, Kudahetti SC, Prowse DM, Ktori E, Cuzick J, Ambroisine L, Zhang X, Watkin N, Corbishley C, Berney DM. HPV infection and immunochemical detection of cell-cycle markers in verrucous carcinoma of the penis. Mod Pathol. 2009;22:1160–8.
28. Masih AS, Stoler MH, Farrow GM, Wooldridge TN, Johansson SL. Penile verrucous carcinoma: a clinicopathologic, human papillomavirus typing and flow cytometric analysis. Mod Pathol. 1992;5:48–55.
29. Mukai S, Nakahara K, Nagai T, Kamibeppu T, Sugie S, Tsukino H, Kamimura T, Wakeda H, Kamoto

T. Pure verrucous carcinoma of the penis: two cases. Med Surg Urol. 2014;3:125–7.
30. Chaux A, Soares F, Rodríguez I, Barreto J, Lezcano C, Torres J, Velazquez EF, Cubilla AL. Papillary squamous cell carcinoma, not otherwise specified (NOS) of the penis: clinicopathologic features, differential diagnosis, and outcome of 35 cases. Am J Surg Pathol. 2010;34:223–30.
31. Cubilla AL, Lloveras B, Alejo M, Clavero O, Chaux A, Kasamatsu E, Velazquez EF, Lezcano C, Monfulleda N, Tous S, Alemany L, Klaustermeier J, Muñoz N, Quint W, de Sanjose S, Bosch FX. The basaloid cell is the best tissue marker for human papillomavirus in invasive penile squamous cell carcinoma: a study of 202 cases from Paraguay. Am J Surg Pathol. 2010;34:104–14.
32. 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.
33. Barreto JE, Velazquez EF, Ayala E, Torres J, Cubilla AL. Carcinoma cuniculatum: a distinctive variant of penile squamous cell carcinoma: report of 7 cases. Am J Surg Pathol. 2007;31:71–5.
34. Seehafer JR, Rahman D, Soderstrom CW. Epithelioma cuniculatum: verrucous carcinoma of the foot. Cutis. 1979;23:287–90.
35. Kathuria S, Rieker J, Jablokow VR, Van den Broek H. Plantar verrucous carcinoma (epithelioma cuniculatum): case report with review of the literature. J Surg Oncol. 1986;31:71–5.
36. Reuter VE. Sarcomatoid lesions of the urogenital tract. Semin Diagn Pathol. 1993;10:188–201.
37. 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;28:384–9.
38. Velazquez EF, Melamed J, Barreto JE, Aguero F, Cubilla AL. Sarcomatoid carcinoma of the penis: a clinicopathologic study of 15 cases. Am J Surg Pathol. 2005;29:1152–8.
39. Cubilla AL, Reuter VE, Gregoire L, Ayala G, Ocampos S, Lancaster WD, Fair W. Basaloid squamous cell carcinoma: a distinctive human papilloma virus-related penile neoplasm: a report of 20 cases. Am J Surg Pathol. 1998;22:755–61.
40. Soskin A, Vieillefond A, Carlotti A, Plantier F, Chaux A, Ayala G, Velazquez EF, Cubilla AL. Warty/basaloid penile intraepithelial neoplasia is more prevalent than differentiated penile intraepithelial neoplasia in nonendemic regions for penile cancer when compared with endemic areas: a comparative study between pathologic series from Paris and Paraguay. Hum Pathol. 2012;43:190–6.
41. Winters R, Trotman W, Adamson CS, Rajendran V, Tang A, Elhosseiny A, Evans MF. Screening for human papillomavirus in basaloid squamous carcinoma: utility of p16(INK4a), CISH, and PCR. Int J Surg Pathol. 2011;19:309–14.
42. Cubilla AL, Lloveras B, Alemany L, Alejo M, Vidal A, Kasamatsu E, Clavero O, Alvarado-Cabrero I, Lynch C, Velasco-Alonso J, Ferrera A, Chaux A, Klaustermeier J, Quint W, de Sanjosé S, Muñoz N, Bosch FX. Basaloid squamous cell carcinoma of the penis with papillary features: a clinicopathologic study of 12 cases. Am J Surg Pathol. 2012;36:869–75.
43. Rubin MA, Kleter B, Zhou M, Ayala G, Cubilla AL, Quint WG, Pirog EC. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. Am J Pathol. 2001;159:1211–8.
44. Cubilla AL, Velazquez EF, Young RH. Pseudohyperplastic squamous cell carcinoma of the penis associated with lichen sclerosus. An extremely well-differentiated, nonverruciform neoplasm that preferentially affects the foreskin and is frequently misdiagnosed: a report of 10 cases of a distinctive clinicopathologic entity. Am J Surg Pathol. 2004;28:895–900.
45. Cunha IW, Guimaraes GC, Soares F, Velazquez E, Torres JJ, Chaux A, Ayala G, Cubilla AL. Pseudoglandular (adenoid, acantholytic) penile squamous cell carcinoma: a clinicopathologic and outcome study of 7 patients. Am J Surg Pathol. 2009;33:551–5.
46. Colecchia M, Insabato L. Pseudoglandular (adenoid, acantholytic) penile squamous cell carcinoma. Am J Surg Pathol. 2009;33:1421–2.
47. Cubilla AL, Ayala MT, Barreto JE, Bellasai JG, Nöel JC. Surface adenosquamous carcinoma of the penis. A report of three cases. Am J Surg Pathol. 1996;20:156–60.
48. Masera A, Ovcak Z, Volavsek M, Bracko M. Adenosquamous carcinoma of the penis. J Urol. 1997;157:2261.
49. Chaux A, Tamboli P, Ayala A, Soares F, Rodríguez I, Barreto J, Cubilla AL. Warty-basaloid carcinoma: clinicopathological features of a distinctive penile neoplasm. Report of 45 cases. Mod Pathol. 2010;23:896–904.
50. Chaux A, Pfannl R, Lloveras B, Alejo M, Clavero O, Lezcano C, Muñoz N, de Sanjosé S, Bosch X, Hernández-Pérez M, Velazquez EF, Cubilla AL. Distinctive association of p16INK4a overexpression with penile intraepithelial neoplasia depicting warty and/or basaloid features: a study of 141 cases evaluating a new nomenclature. Am J Surg Pathol. 2010;34:385–92.
51. Kato N, Onozuka T, Yasukawa K, Kimura K, Sasaki K. Penile hybrid verrucous-squamous carcinoma associated with a superficial inguinal lymph node metastasis. Am J Dermatopathol. 2000;22:339–43.
52. Velazquez EF, Ayala G, Liu H, Chaux A, Zanotti M, Torres J, Cho SI, Barreto JE, Soares F, Cubilla 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;32:974–9.
53. IARC Monograph Working Group. A review of human carcinogens-Part B: biological agents. Lancet Oncol. 2009;10:321–2.
54. Lont AP, Kroon BK, Horenblas S, Gallee MP, Berkhof J, Meijer CJ, Snijders PJ. Presence of high-risk human papillomavirus DNA in penile carcinoma predicts favorable outcome in survival. Int J Cancer. 2006;119:1078–81.
55. Ferreux E, Lont AP, Horenblas S, Gallee MP, Raaphorst FM, von Knebel Doeberitz M, Meijer CJ, Snijders PJ. Evidence for at least three alternative mechanisms targeting the p16INK4A/cyclin D/Rb pathway in penile carcinoma, one of which is mediated by high-risk human papillomavirus. J Pathol. 2003;201:109–18.
56. Sano T, Oyama T, Kashiwabara K, Fukuda T, Nakajima T. Expression status of p16 protein is associated with human papillomavirus oncogenic potential in cervical and genital lesions. Am J Pathol. 1998;153:1741–8.
57. Chaux A, Cubilla AL, Haffner MC, Lecksell KL, Sharma R, Burnett AL, Netto GJ. Combining routine morphology, p16(INK4a) immunohistochemistry, and in situ hybridization for the detection of human papillomavirus infection in penile carcinomas: a tissue microarray study using classifier performance analyses. Urol Oncol. 2014;32:171–7.
58. Bezerra AL, Lopes A, Santiago GH, Ribeiro KC, Latorre MR, Villa LL. Human papillomavirus as a prognostic factor in carcinoma of the penis: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. Cancer. 2001;91:2315–21.
59. Gunia S, Erbersdobler A, Hakenberg OW, Koch S, May M. p16(INK4a) is a marker of good prognosis for primary invasive penile squamous cell carcinoma: a multi-institutional study. J Urol. 2012;187:899–907.
60. Djajadiningrat RS, Jordanova ES, Kroon BK, van Werkhoven E, de Jong J, Pronk DT, Snijders PJ, Horenblas S, Heideman DA. Human papillomavirus prevalence in invasive penile cancer and association with clinical outcome. J Urol. 2015;193:526–31.
61. Bezerra SM, Chaux A, Ball MW, Faraj SF, Munari E, Gonzalez-Roibon N, Sharma R, Bivalacqua TJ, Burnett AL, Netto GJ. Human papillomavirus infection and immunohistochemical p16(INK4a) expression as predictors of outcome in penile squamous cell carcinomas. Hum Pathol. 2015;46:532–40.
62. Stankiewicz E, Prowse DM, Ng M, Cuzick J, Mesher D, Hiscock F, Lu YJ, Watkin N, Corbishley C, Lam W, Berney DM. Alternative HER/PTEN/Akt pathway activation in HPV positive and negative penile carcinomas. PLoS One. 2011;6:e17517.
63. Necchi A, Nicolai N, Colecchia M, Catanzaro M, Torelli T, Piva L, Salvioni R. Proof of activity of anti-epidermal growth factor receptor-targeted therapy for relapsed squamous cell carcinoma of the penis. J Clin Oncol. 2011;29:e650–2.
64. Lam KY, Chan KW. Molecular pathology and clinicopathologic features of penile tumors: with special reference to analyses of p21 and p53 expression and unusual histologic features. Arch Pathol Lab Med. 1999;123:895–904.
65. Lopes A, Bezerra AL, Pinto CA, Serrano SV, de MellO CA, Villa LL. p53 as a new prognostic factor for lymph node metastasis in penile carcinoma: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. J Urol. 2002;168:81–6.
66. Chaux A, Munari E, Cubilla AL, Hicks J, Lecksell K, Burnett AL, Netto GJ. Immunohistochemical expression of the mammalian target of rapamycin pathway in penile squamous cell carcinomas: a tissue microarray study of 112 cases. Histopathology. 2014;64:863–71.
67. Alves G, Heller A, Fiedler W, Campos MM, Claussen U, Ornellas AA, Liehr T. Genetic imbalances in 26 cases of penile squamous cell carcinoma. Genes Chromosomes Cancer. 2001;31:48–53.
68. Berney D. Molecular aspects of carcinoma of the penis. The science. Abstract SC-03-002 26 European Congress of Pathology. London, 2014.
69. Campos RS, Lopes A, Guimarães GC, Carvalho AL, Soares FA. E-cadherin, MMP-2, and MMP-9 as prognostic markers in penile cancer: analysis of 125 patients. Urology. 2006;67:797–802.
70. Graafland NM, Lam W, Leijte JA, Yap T, Gallee MP, Corbishley C, van Werkhoven E, Watkin N, Horenblas S. Prognostic factors for occult inguinal lymph node involvement in penile carcinoma and assessment of the high-risk EAU subgroup: a two-institution analysis of 342 clinically node-negative patients. Eur Urol. 2010;58:742–7.
71. 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;4:140–6.
72. 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;177:947–52.
73. Johnson TV, Hsiao W, Delman KA, Jani AB, Brawley OW, Master VA. Extensive inguinal lymphadenectomy improves overall 5-year survival in penile cancer patients: results from the Surveillance, Epidemiology, and End Results program. Cancer. 2010;116:2960–6.
74. Lughezzani G, Catanzaro M, Torelli T, Piva L, Biasoni D, Stagni S, Crestani A, Guttilla A, Raggi D, Giannatempo P, Necchi A, Pizzocaro G, Colecchia M, Salvioni R, Nicolai N. The relationship between characteristics of inguinal lymph nodes and pelvic lymph node involvement in penile squamous cell carcinoma: a single institution experience. J Urol. 2014;191:977–82.
75. Horenblas S, van Tinteren H. Squamous cell carcinoma of the penis. IV. Prognostic factors of survival:

analysis of tumor, nodes and metastasis classification system. J Urol. 1994;151:1239–43.
76. Chaux A, Torres J, Pfannl R, Barreto J, Rodriguez I, Velazquez EF, Cubilla 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;33:1042–8.
77. 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;14:963–8.
78. Cubilla AL. The role of pathologic prognostic factors in squamous cell carcinoma of the penis. World J Urol. 2009;27:169–77.
79. 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 examination of 44 cases. Am J Surg Pathol. 2001;25:1091–4.
80. Chaux A, Caballero C, Soares F, Guimarães GC, Cunha IW, Reuter V, Barreto J, Rodríguez I, Cubilla 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;33:1049–57.
81. Slaton JW, Morgenstern N, Levy DA, Santos Jr MW, Tamboli P, Ro JY, Ayala AG, Pettaway CA. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal lymph node metastasis in penile squamous cancer. J Urol. 2001;165:1138–42.
82. Ficarra V, Zattoni F, Cunico SC, Galetti TP, Luciani L, Fandella A, Guazzieri S, Maruzzi D, Sava T, Siracusano S, Pilloni S, Tasca A, Martignoni G, Gardiman M, Tardanico R, Zambolin T, Cisternino A, Artibani W, Gruppo Uro-Oncologico del Nord Est (Northeast Uro-Oncological Group) Penile Cancer Project. Lymphatic and vascular embolizations are independent predictive variables of inguinal lymph 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;103:2507–16.
83. Guimarães GC, Lopes A, Campos RS, Zequi Sde C, Leal ML, Carvalho AL, da Cunha IW, Soares FA. Front pattern of invasion in squamous cell carcinoma of the penis: new prognostic factor for predicting risk of lymph node metastases. Urology. 2006;68:148–53.
84. Guimarães GC, Leal ML, Campos RS, Zequi Sde C, da Fonseca FP, da Cunha IW, Soares FA, Lopes A. Do proliferating cell nuclear antigen and MIB-1/Ki-67 have prognostic value in penile squamous cell carcinoma? Urology. 2007;70:137–42.
85. Kroon BK, Leijte JA, van Boven H, Wessels LF, Velds A, Horenblas S, van't Veer LJ. Microarray gene-expression profiling to predict lymph node metastasis in penile carcinoma. BJU Int. 2008;102:510–5.
86. Ficarra V, Zattoni F, Artibani W, Fandella A, Martignoni G, Novara G, Galetti TP, Zambolin T, Kattan MW, G.U.O.N.E. Penile Cancer Project Members. Nomogram predictive of pathological inguinal lymph node involvement in patients with squamous cell carcinoma of the penis. J Urol. 2006;175:1700–4.
87. Kattan MW, Ficarra V, Artibani W, Cunico SC, Fandella A, Martignoni G, Fandella A, Novara G, Galetti TP, Zattoni F, 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;175:2103–8.
88. UICC. TNM classification of malignant tumours. 7th ed. New York: Wiley & Sons; 2009.
89. Protzel C, Knoedel J, Zimmermann U, Woenckhaus C, Poetsch M, Giebel J. Expression of proliferation marker Ki67 correlates to occurrence of metastasis and prognosis, histological subtypes and HPV DNA detection in penile carcinomas. Histol Histopathol. 2007;22:1197–204.
90. Zhu Y, Zhou XY, Yao XD, Dai B, Ye DW. The prognostic significance of p53, Ki-67, epithelial cadherin and matrix metalloproteinase-9 in penile squamous cell carcinoma treated with surgery. BJU Int. 2007;100:204–8.
91. Van Poppel H, Watkin NA, Osanto S, Moonen L, Horwich A, Kataja V, ESMO Guidelines Working Group. Penile cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24:vi115–24.
92. Protzel C, Kakies C, Kleist B, Poetsch M, Giebel J. Down-regulation of the metastasis suppressor protein KAI1/CD82 correlates with occurrence of metastasis, prognosis and presence of HPV DNA in human penile squamous cell carcinoma. Virchows Arch. 2008;452:369–75.
93. Termini L, Fregnani JH, Boccardo E, da Costa WH, Longatto-Filho A, Andreoli MA, Costa MC, Lopes A, da Cunha IW, Soares FA, Villa LL, Guimarães GC. SOD2 immunoexpression predicts lymph node metastasis in penile cancer. BMC Clin Pathol. 2015;15:3–8.
94. Alves G, Fiedler W, Guenther E, Nascimento P, Campos MM, Ornellas AA. Determination of telomerase activity in squamous cell carcinoma of the penis. Int J Oncol. 2001;18:67–70.
95. Hungerhuber E, Schlenker B, Schneede P, Stief CG, Karl A. Squamous cell carcinoma antigen correlates with tumor burden but lacks prognostic potential for occult lymph node metastases in penile cancer. Urology. 2007;70:975–9.
96. Golijanin D, Tan JY, Kazior A, Cohen EG, Russo P, Dalbagni G, Auborn KJ, Subbaramaiah K, Dannenberg AJ. Cyclooxygenase-2 and microsomal prostaglandin E synthase-1 are overexpressed in

squamous cell carcinoma of the penis. Clin Cancer Res. 2004;10:1024–31.
97. Muneer A, Kayes O, Ahmed HU, Arya M, Minhas S. Molecular prognostic factors in penile cancer. World J Urol. 2009;27:161–7.
98. Amin A, Griffith RC, Chaux A. Penile intraepithelial neoplasia with pagetoid features: report of an unusual variant mimicking Paget disease. Hum Pathol. 2014;45:889–92.
99. Leijte JA, Kroon BK, Valdés Olmos RA, Nieweg OE, Horenblas S. Reliability and safety of current dynamic sentinel node biopsy for penile carcinoma. Eur Urol. 2007;52:170–7.
100. Leijte JA, Hughes B, Graafland NM, Kroon BK, Olmos RA, Nieweg OE, Corbishley C, Heenan S, Watkin N, Horenblas S. Two-center evaluation of dynamic sentinel node biopsy for squamous cell carcinoma of the penis. J Clin Oncol. 2009;27:3325–9.
101. Chaux A, Reuter V, Lezcano C, Velazquez EF, Torres J, Cubilla AL. Comparison of morphologic features and outcome of resected recurrent and nonrecurrent squamous cell carcinoma of the penis: a study of 81 cases. Am J Surg Pathol. 2009;33:1299–306.
102. Lont AP, Gallee MP, Meinhardt W, van Tinteren H, Horenblas S. Penis conserving treatment for T1 and T2 penile carcinoma: clinical implications of a local recurrence. J Urol. 2006;176:575–80.
103. Hoffman MA, Renshaw AA, Loughlin KR. Squamous cell carcinoma of the penis and microscopic pathologic margins: how much margin is needed for local cure? Cancer. 1999;85:1565–8.
104. Leijte JA, Kirrander P, Antonini N, Windahl T, Horenblas S. Recurrence patterns of squamous cell carcinoma of the penis: recommendations for follow-up based on a two-centre analysis of 700 patients. Eur Urol. 2008;54:161–9.
105. Liegl B, Regauer S. Penile clear cell carcinoma: a report of 5 cases of a distinct entity. Am J Surg Pathol. 2004;28:1513–7.
106. Lopez-Beltran A, Menendez CL, Montironi R, Cheng L. Rare tumors and tumor-like conditions in urological pathology. Switzerland: Springer International Publishing; 2015. p. 410.
107. Smith KJ, Tuur S, Corvette D, Lupton GP, Skelton HG. Cytokeratin 7 staining in mammary and extramammary Paget's disease. Mod Pathol. 1997;10:1069–74.
108. Liegl B, Leibl S, Gogg-Kamerer M, Tessaro B, Horn LC, Moinfar F. Mammary and extramammary Paget's disease: an immunohistochemical study of 83 cases. Histopathology. 2007;50:439–47.
109. Lee JY. Clear cell papulosis: a unique disorder in early childhood characterized by white macules in milk-line distribution. Pediatr Dermatol. 1998;15:328–9.
110. Sánchez-Ortiz R, Huang SF, Tamboli P, Prieto VG, Hester G, Pettaway CA. Melanoma of the penis, scrotum and male urethra: a 40-year single institution experience. J Urol. 2005;173:1958–65.
111. van Geel AN, den Bakker MA, Kirkels W, Horenblas S, Kroon BB, de Wilt JH, Eggermont AM, Mooi WJ, van der Aa MN. Prognosis of primary mucosal penile melanoma: a series of 19 Dutch patients and 47 patients from the literature. Urology. 2007;70:143–7.
112. Zurrida S, Bartoli C, Clemente C, De Palo G. Malignant melanoma of the penis. A report of four cases. Tumori. 1990;76:599–602.
113. Barnhill RL, Albert LS, Shama SK, Goldenhersh MA, Rhodes AR, Sober AJ. Genital lentiginosis: a clinical and histopathologic study. J Am Acad Dermatol. 1990;22:453–60.
114. Katona TM, Lopez-Beltran A, MacLennan GT, Cheng L, Montironi R, Cheng L. Soft tissue tumors of the penis: a review. Anal Quant Cytol Histol. 2006;28:193–206.
115. Fetsch JF, Sesterhenn IA, Miettinen M, Davis Jr CJ. Epithelioid hemangioma of the penis: a clinicopathologic and immunohistochemical analysis of 19 cases, with special reference to exuberant examples often confused with epithelioid hemangioendothelioma and epithelioid angiosarcoma. Am J Surg Pathol. 2004;28:523–33.
116. Fetsch JF, Brinsko RW, Davis Jr CJ, Mostofi FK, Sesterhenn IA. A distinctive myointimal proliferation ('myointimoma') involving the corpus spongiosum of the glans penis: a clinicopathologic and immunohistochemical analysis of 10 cases. Am J Surg Pathol. 2000;24:1524–30.
117. McKenney JK, Collins MH, Carretero AP, Boyd TK, Redman JF, Parham DM. Penile myointimoma in children and adolescents: a clinicopathologic study of 5 cases supporting a distinct entity. Am J Surg Pathol. 2007;31:1622–6.
118. Lowe FC, Lattimer DG, Metroka CE. Kaposi's sarcoma of the penis in patients with acquired immunodeficiency syndrome. J Urol. 1989;142:1475–7.
119. Micali G, Nasca MR, De Pasquale R, Innocenzi D. Primary classic Kaposi's sarcoma of the penis: report of a case and review. J Eur Acad Dermatol Venereol. 2003;17:320–3.
120. Dehner LP, Smith BH. Soft tissue tumors of the penis. A clinicopathologic study of 46 cases. Cancer. 1970;25:1431–47.
121. Fetsch JF, Davis Jr CJ, Miettinen M, Sesterhenn IA. Leiomyosarcoma of the penis: a clinicopathologic study of 14 cases with review of the literature and discussion of the differential diagnosis. Am J Surg Pathol. 2004;28:115–25.
122. Antunes AA, Nesrallah LJ, Goncalves PD, Ferreira YA, Campagnari JC, Srougi M. Deep-seated sarcomas of the penis. Int Braz J Urol. 2005;31:245–50.
123. Usta MF, Adams DM, Zhang JW, Davis R, Hellstrom WJ. Penile epithelioid sarcoma and the case for a histopathological diagnosis in Peyronie's disease. BJU Int. 2003;91:519–21.
124. Rossi G, Ferrari G, Longo L, Trentini GP. Epithelioid sarcoma of the penis: a case report and review of the literature. Pathol Int. 2000;50:579–85.
125. Lowentritt B, Parsons JK, Argani P, Gearhart JP. Pediatric epithelioid sarcoma of the penis. J Urol. 2004;172:296–7.

126. Ponniah A, Brown CT, Taylor P. Priapism secondary to leukemia: effective management with prompt leukapheresis. Int J Urol. 2004;11:809–10.
127. Arena F, di Stefano C, Peracchia G, Barbieri A, Cortellini P. Primary lymphoma of the penis: diagnosis and treatment. Eur Urol. 2001;39:232–5.
128. Hizli F, Berkmen F. Penile metastasis from other malignancies. A study of ten cases and review of the literature. Urol Int. 2006;76:118–21.
129. Chaux A, Amin M, Cubilla AL, Young RH. Metastatic tumors to the penis: a report of 17 cases and review of the literature. Int J Surg Pathol. 2011;19:597–606.
130. Celma Doménech A, Planas Morin J, de Torres Ramírez I, Bestard Vallejo J, Mir Marisma C, Morote Robles J. Priapism secondary to penis infiltration of bladder cancer. Actas Urol Esp. 2008;32:749–51.
131. Gelbard MK, Dorey F, James K. The natural history of Peyronie's disease. J Urol. 1990;144:1376–9.
132. Leopardi O, Colombo F, Frigo B, Zucchi A, Patelli E, Colecchia M, Mantovani F, Naughten W, Pisani E. Immunohistochemical and quantitative study of mast cells in La Peyronie's disease. Eur Urol. 2000;37:176–82.
133. Abdel-Hamid IA, Anis T. Peyronie's disease: perspectives on therapeutic targets. Expert Opin Ther Targets. 2011;15:913–29.
134. Shen S, Truong LD, Ro JY. Frozen section library: genitourinary tract. Chapter 3. London/New York: Springer; 2009.
135. Cabanas RM. The concept of the sentinel lymph node. Recent Results Cancer Res. 2000;157:109–20.
136. Algaba F, Arce Y, López-Beltrán A, Montironi R, Mikuz G, Bono AV, European Society of Uropathology; Uropathology Working Group. Intraoperative frozen section diagnosis in urological oncology. Eur Urol. 2005;47:129–36.
137. Mukherjee S. The emperor of all maladies. A biography of cancer. New York: Simon and Shuster; 2010.
138. Crocker HR. Paget's disease affecting the scrotum and penis. Trans Pathol Soc Lond. 1889;40:187–91.
139. Park S, Grossfeld GD, McAninch JW, Santucci R. Extramammary Paget's disease of the penis and scrotum: excision, reconstruction and evaluation of occult malignancy. J Urol. 2001;166:2112–7.
140. Terada T, Kamo M, Sugiura M. Apocrine carcinoma of the scrotum with extramammary Paget's disease. Int J Dermatol. 2013;52:504–6.
141. Wright JL, Morgan TM, Lin DW. Primary scrotal cancer: disease characteristics and increasing incidence. Urology. 2008;72:1139–43.
142. Froehner M, Koch R, Lossnitzer A, Schober RR, Schuler M, Wirth MP. Adult inguinoscrotal sarcomas: outcome analysis of 21 cases, systematic review of the literature and meta-analysis. World J Urol. 2014;32:445–51.
143. Johnson TV, Hsiao W, Delman KA, Canter DJ, Master VA. Scrotal cancer survival is influenced by histology: a SEER study. World J Urol. 2013;31:585–90.