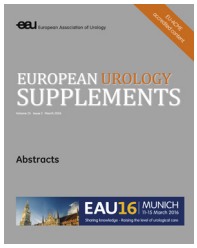
EUROPEAN UROLOGY SUPPLEMENTS XXX (2017) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



European Association of Urology

Pathology of Penile Cancer

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Article info

Keywords:
Pathology
Squamous cell carcinoma
Human papilloma virus

Abstract

The majority of malignant tumors of the penis are squamous cell carcinomas. The origin is mostly the inner lining of the mucosa of the glans, the coronal sulcus, and the foreskin. Other tumors, such as basal cell carcinoma, are very rare. Numerous different subtypes have been reported and have been integrated into the new World Health Organization 2016 classification. These subtypes have distinct features and outcomes, and it is important to make the difference from a pathological point of view. During the last 2 decades, major progress has been made and it has become obvious that human papilloma virus (HPV) infection plays a major role. Mostly the morphological aspects will lead the pathologist to classify the carcinoma into HPV-related and nonrelated carcinoma. Although polymerase chain reaction is the gold standard for HPV detection, immunohistochemistry is also useful. These tumors have to be staged according to the pTNM system; nevertheless, two different systems exist, and the pathologist should tell whether he/she uses the European (Union for International Cancer Control) or the American (American Joint Committee on Cancer) staging system.

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1. Epidemiology

Penile carcinoma affects most often patients in their 5th or 6th decade, but they can occur in younger and older age. Familial cases are rare. No racial predilection has been described. The highest incidence rates are observed in South America, Asia, and Africa; the incidence is relatively low in Europe and North America. Penile carcinoma accounts for 0.4–0.6% of malignancies [1]. The incidence has been slightly decreasing in some countries, but human papilloma virus (HPV)–related tumors increase in several countries such as the USA. Risk factors such as lack of neonatal circumcision, poor genital hygiene, phimosis, HPV infection, lichen sclerosus, and smoking are well known [2]. Obesity also seems to play a role [3,4].

It is crucial to have good knowledge of the very complex anatomy of the penis. In the distal penis, three different epithelial mucosa compartments exist: glans, coronal sulcus, and foreskin. Different anatomic levels in the glans are the lamina propria, corpus spongiosum, tunica albuginea, and corpus cavernosum. The foreskin has an inner mucosa and a surface skin, both different from a histological point of view. The anatomical levels from the mucosa to the skin are lamina propria, dartos, dermis, and epidermis. The penile fascia covers the shaft and inserts into the lamina propria of the coronal sulcus. The fossa navicularis corresponds to the distal penile urethra; its squamous lining is continuous with the perimeatal glans. The penile urethra is ventral, and surrounded by a lamina propria corpus spongiosum and a penile fascia.

http://dx.doi.org/10.1016/j.eursup.2017.08.005
1569-9056/

2. Histopathology

It is important to distinguish precursor lesions from malignant tumors; premalignant lesions, similar to malignant lesions, can be divided into HPV-related and non–HPV-related groups.

2.1. Precursor lesions

2.1.1. Penile intraepithelial neoplasms

In this setting, the basement membrane remains intact, but intraepithelial changes occur. A penile intraepithelial neoplasm (PeIN) is a recognized precursor of invasive squamous cell carcinoma (SCC).

Like in case of invasive carcinomas, two subgroups can be distinguished: HPV-related and non–HPV-related PeIN. Mostly there exists a good correlation between the grade of PeIN and the differentiation of SCC. The same is true for warty/basaloid PeIN.

Precursor lesions are mostly seen in patients between 40 and 70 yr of age. Their size can vary from small millimetric ones to widespread lesions. Differentiated PeINs are frequently seen with lichen sclerosus. It affects the foreskin; the warty–basaloid type affects the glans more frequently [5].

On gross examination, solitary white or pink maculae or plaques can be observed, borders can be sharp or irregular, and solitary or multifocal lesions are possible. The warty–basaloid PeIN has more velvet-like moist dark brown aspects.

Under the microscope, differentiated PeIN looks like thickened skin; keratin pearl forming and parakeratosis are frequent. In simplex (differentiated) PeIN, atypia exists in the basal layer. The higher the atypia takes place in the epithelium, the higher is the risk of developing an invasive carcinoma. Grading PeIN is optional. It has to be underlined that lichen sclerosus is often associated with PeIN. The difference between a PeIN and a reactive condition can be very difficult to establish.

Basaloid PeIN is characterized by the replacement of the whole thickness of the epithelial layer by small monotonous cells. Apoptosis and mitosis are common; these lesions are HPV positive [6]. Warty PeIN displays atypical parakeratosis. Cellular pleomorphism, koilocytes, and mitosis are usual. These lesions are also HPV positive. It is unknown to which percentage these lesions evolve toward an infiltrating carcinoma.

Extramammary Paget disease can also be observed. This rare, slowly growing adenocarcinoma can affect the penile skin or surface, mostly scrotal perianal or perineal. Erosive plaques can be misdiagnosed as eczema and can be very large lesions including the pubic region.

Under a microscope, an intraepithelial lesion can be observed; sometimes neoplastic cells contain melanin. When excised completely, prognosis is favorable. In case of dermal invasion, the prognosis becomes more severe [5].

2.2. Malignant epithelial tumors

The most frequent entity is the SCC (Fig. 1). Most of them occur from the inner foreskin, inner lining of the glans, and coronal sulcus. Anatomy is important for the staging of penile carcinomas. Most penile carcinomas originate from the mucosa and not from the skin.

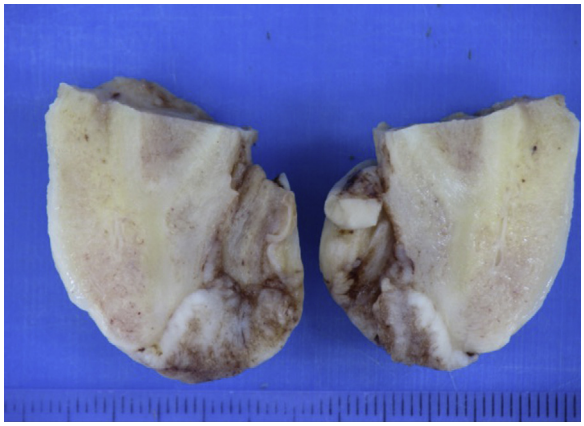

Fig. 1 – Squamous cell carcinoma NOS developing on the foreskin and glans, glansectomy. NOS = not otherwise specified.

According to pathological classification, penile squamous carcinomas are divided into two subgroups: non–HPV-and HPV-related SCCs [7] (see Table 1).

The relationship between HPV and penile carcinoma was first recognized in 1995 [8]. Tumors with basal and/or warty morphology display HPV more frequently. On the contrary, it is rare in usual and low-grade variants of keratinizing SCC and constantly negative in differentiated PeIN [5].

SCC can occur in any part of the penis and can be multifocal. Little is known about its genetic features. Two pathways exist in the carcinogenesis; one is related to HPV, which occurs in about 30–50% of cases. The second, non–HPV-related pathway, can be divided into two subgroups: TP53 mutations and the other with chromosomic instability [7].

2.2.1. Non–HPV-related SCC

2.2.1.1. SCC usual type/not otherwise specified. These carcinomas display the usual aspects of SCC with different degrees of differentiation and keratinization; this diagnosis can be proposed if all the other histological variants have been excluded. Most of the time these tumors have an exophytic gross appearance; endophytic ulcerated cases have also been described.

The grading, like in many other tumors, is a very important prognostic factor. The three-tiered International Society of Urological Pathology/World Health Organization system should be used [7]. The admitted grades range from well to poorly differentiated with different nuclear polymorphisms, atypia, and keratinization (see Table 2). If well differentiated (grade 1), the aspect is the same as keratinizing tissue, they grow in large sheets and can have nested patterns, and the stroma reaction is limited. In moderately differentiated (grade 2) carcinomas, the nests become smaller and the tumor stroma is more abundant. In poorly differentiated (grade 3) tumors, keratinization can be difficult to find, growth is angular and irregular, and mitosis is frequent. As soon as a tumor displays anaplasia, it

Please cite this article in press as: Compérat E, Pathology of Penile Cancer. Eur Urol Suppl (2017), http://dx.doi.org/10.1016/j.eursup.2017.08.005