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Human Papilloma Virus, Histopathological, and Molecular Subtyping in Penile Cancer: Relevance for Prognosis and Therapy

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Article info

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Abstract

Context: Based on the new 2016 World Health Organization classification, penile carcinomas are subdivided into several histopathological subtypes which are associated with human papilloma virus (HPV) infection status.
Objective: The primary objective of this review is to describe the subtyping of penile carcinomas according to the new World Health Organization classification based on HPV infection status and histopathological features and to correlate this to patient outcome. In addition, the current knowledge about the role of HPV infection in tumorigenesis as well as relevant molecular alterations will be presented.
Evidence acquisition: A systematic literature search was conducted using PubMed to identify original articles, review articles regarding penile cancer/carcinoma, HPV, histopathological subtypes, prognosis, and molecular alterations. Articles published between 1989 and 2017 were reviewed and selected with the consensus of all the authors.
Evidence synthesis: Penile squamous cell carcinomas (SCC) are the most common penile tumours. They are divided into HPV-related and HPV-unrelated subtypes based on the frequency of high-risk HPV infection. Histopathological subtype but not the HPV-status alone is associated with clinical outcome. High-risk HPV infection occurs in about 50% of penile SCC and varies worldwide. Although some specific molecular alterations including copy number alterations or mutations (most frequently *CDKN2A* and *p53*) and changes in signalling pathways could be identified, molecular pathogenesis considering HPV infection is not fully understand.
Conclusions: The histopathological subtype should be documented and considered for prognostic evaluation in patients with penile SCC. The prognostic value of HPV infection has to be investigated in larger cohorts considering the histopathological subtype. Further molecular studies have to identify relevant molecular subtypes and to develop type-specific targeted therapies.

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1. Introduction

Penile cancer is a rare disease but its frequency varies in different countries. The highest incidence is reported in Africa, Asia, and South America (2–4/100 000), the lowest in European countries and in the USA (0.3–1.1/100000) [1,2]. Poor hygiene, phimosis, chronic inflammation like lichen sclerosus, smoking, and human papilloma virus (HPV) infection are risk factors [3,4]. Circumcision in young children but not in adults reduces the risk of penile cancer [5–7]. Survival for penile cancer patients has not improved in either Europe or the USA since at least 1990 [8]. One reason is the lack of effective systemic therapies in metastatic disease due to the lack of clinical trials in this rare disease. Furthermore, only little is known about the signalling pathways activated in this tumour entity.

About 30–63% of penile carcinomas are associated with HPV infection [3,9–11]. This large variation might be caused by small series, geographic regions of included patients, different HPV detection methods, and histopathological subtype composition of cohorts [12]. The most prevalent high-risk genotype is HPV 16 (72–76%) followed by 18, 33, and 45 with much lower frequencies [11,13]. Although a better disease-specific survival has been reported for HPV-positive versus HPV-negative cases, data are contradictory [13–15].

This review describes the new World Health Organization (WHO) classification, the role of HPV in tumorigenesis and the molecular alterations of penile squamous cell carcinomas (SCCs).

2. Evidence acquisition

A systematic literature search was conducted using PubMed to identify original articles, review articles regarding penile cancer, HPV, histopathological subtypes, prognosis, and molecular alterations. Articles published between 1989 and 2017 were reviewed and selected with the consensus of all the authors.

3. Evidence synthesis

3.1. Histopathological classification and relation to HPV infection

The new 2016 WHO Classifications introduced a new classification of penile tumours which is based on clinicopathological and morphological features and strongly related to HPV infection [16]. Fig. 1

The majority of malignant tumors of the penis are SCCs. The new classification system goes beyond pure histomorphological characterisation of the tumour and is based on the findings that specific histopathological subtypes of penile carcinoma are frequently related to HPV infection (Table 1).

3.1.1. Non-HPV-related SCC

The histological type of penile carcinoma is strongly associated with prognosis [17].

About half of penile SCCs are of the *usual type* presenting conventional squamous histology. These tumours are frequently HPV negative, although 10–20% can be related to HPV infection. The prognosis is related to the extent of the disease and the differentiation. Poorly differentiated SCCs with anaplastic cells with nuclear pleomorphism, high nuclear cytoplasmic ratio, prominent nucleoli, and single cell infiltrative growth have a poorer prognosis. To take the importance of grading in penile SCC into account, poor differentiation was included in the recent Tumor/Node/Metastasis classification. However, the reproducibility of histopathological tumour grading in penile cancer is poor [18]. Therefore, new molecular methods to reliably predict prognoses are urgently needed. Other histopathological factors associated with poorer prognosis are perineural invasion, vascular invasion, tumour thickness more than 10 mm, deep infiltration in the corpus spongiosum or corpora cavernosa, and vertical growth pattern [19].

Verrucous carcinomas are exophytic verrucous lesions with papillomatous growth and extremely good differentiation. Recurrences are reported in a third of cases but metastases do not occur if tumours are noninvasive and well differentiated, as found in the majority of cases [20]. Focal invasion does not affect prognosis. These tumours are nearly always HPV negative [21].

Carcinoma cuniculatum is a very infrequent variant of Tis carcinoma characterised by inverted growth pattern with the same good prognosis as verrucous carcinoma.

In contrast, sarcomatoid carcinomas are the frequently HPV-negative histological type with the poorest prognosis [17,20]. They show a biphasic epithelial spindle-cell growth and can simulate various sarcomas.

Pseudoglandular carcinomas are spindle-cell carcinomas with acantholytic or adenoid features and frequent central necrosis within tumour nests. They are usually high grade, frequently HPV negative, and have a very poor prognosis [22].

In contrast, pseudohyperplastic carcinomas are a histological tumour type with excellent prognosis. They occur mainly on the foreskin of older men with a long-standing history of lichen sclerosus. They show low-grade histology and a pseudohyperplastic growth with a pseudo-epitheliomatous, frequently multicentric hyperplastic growth of squamous epithelium. HPV is negative in all cases, metastases were not observed yet [23].

3.1.2. HPV-related SCC

HPV-positive tumours often show a very specific histopathology. The most frequent HPV-related tumour type is *basaloid* SCC. It accounts for 10–15% of all penile carcinomas and is HPV positive in 80% of the cases. HPV-16 is the most commonly found serotype. The tumour is characterised by deeply infiltrating tumour nests with small-to-medium size tumour cells with basophylic cytoplasm and basaloid appearance. Tumours are mostly deeply infiltrating and the prognosis is poor with mortality rates between 20% and 70% [17,24]. Inguinal nodal metastases are frequent (50–100%).

In contrast, *warty* SCC is an HPV-related tumour with a much better prognosis. It accounts for 5–10% of all penile SCCs and is frequently HPV positive. Local recurrences are