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Pathology, Molecular Biology, and Prognosis of Penile Squamous Cell Carcinoma: What Can We Learn from the Specimen?

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Abstract

In the treatment of penile cancer, there is a need for prognostic and predictive factors allowing assessment of the likelihood of lymph node metastasis, as this would greatly facilitate clinical decision-making for invasive staging of inguinal nodes. Furthermore, systemic chemotherapy in metastatic disease has limited efficacy and more effective additional or second-line therapies are needed. There is a great interest in personalised and targeted therapies at present, but do we have any indications that these will be useful in penile cancer? This review examines the well-proven predictors of prognosis that pathologists can take from specimens, and reports which molecular markers are of proven value in penile cancer.

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1. Introduction

Penile cancer is rare in Europe and the USA but much more common in other parts of the world. Treatment is often mutilating and advanced stages with lymph node metastases are life-threatening. Since penile cancer is relatively rare, treatment recommendations are mostly based on small retrospective cohort studies. Despite increased clinical and scientific interest in penile cancer, there has been little progress in the outcomes after penile cancer treatment over the last two decades [1]. However, owing to intensified research into the pathology and molecular biology of penile cancer, we do know more about its aetiology, pathogenesis, and prognosis.

One of the most important questions in recent research has been if there are biological markers in penile cancer that can reliably predict whether an individual penile cancer is likely to metastasise and progress or not. In particular, the propensity for lymph node metastasis is an important clinical question, since the staging of inguinal lymph nodes in patients with clinically normal nodes requires invasive procedures. Prognostic and predictive markers as information that could be derived from examining tumour specimens would greatly improve clinical decision-making.

So what can we learn from the specimen? This paper is reviews the current evidence for the pathological information that tumour specimens can provide and current scientific evidence on markers of progression and prognosis in penile cancer.

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2. Macroscopic pathology of penile cancer

There are different growth patterns of penile cancer. Warty tumours are exophytic, greyish-white lesions with proliferative keratinisation. Superficially spreading carcinomas show a horizontal growth pattern. Vertical tumours are often ulcerated and primarily grow vertically into deeper tissue areas. Variants and mixed forms of these patterns are common. Multicentric carcinomas consist of multifocal and independently growing lesions that have often developed from precursor lesions (see below).

2.1. Histological classification of penile squamous cell carcinoma

Some 95% of penile malignancies are squamous cell carcinomas (SCCs). While this used to be a final diagnosis, the World Health Organisation (WHO) classification clearly differentiates between different histological subtypes of penile SCC since 2016 [2]. These subtypes of penile SCCs differ not only in their histological appearance but also in their clinical course, prognosis, and pathogenesis.

2.2. Aetiology of penile cancer

Approximately 30–40% of penile SCCs are associated with and probably caused by a human papillomavirus (HPV) infection. The incidence of this HPV association varies between different countries worldwide, depending on the regional prevalence of HPV. The WHO classification of penile SCC differentiates between HPV-associated cancers and those not associated with HPV. This new classification thus emphasises the aetiological importance of a HPV infection for the development of some forms of penile SCC. Other well-known aetiological risk factors remain and are considered to be of importance for the development of non–HPV-related penile SCCs. The factors are chronic inflammation, especially chronic balanoposthitis, often related to a phimosis, and lichen sclerosus [3]. Epidemiological studies have also implicated cigarette smoking and sun exposure as cofactors.

2.3. Carcinogenesis in penile cancer

There are HPV-positive and HPV-negative variants of penile cancer. It therefore seems likely that there are two different penile carcinogenesis pathways. One seems to be related to (and perhaps induced by) HPV infection, while the other seems to be related to chronic inflammatory conditions (most commonly chronic balanoposthitis with chronic phimosis). HPV-related and non–HPV-related penile carcinomas show differences in their histology (see above) and, it is assumed, in their molecular carcinogenetic pathways as well. However, it is also likely that they share some carcinogenetic signal pathways.

In HPV-related carcinogenesis of penile cancer, inactivation of cellular tumour suppressor genes is effected by viral oncogenes. The overexpression of two viral oncogenes (*E6* and *E7*) results in point mutation of the tumour suppressor genes *TP53* and retinoblastoma gene *RbE2F*. This leads to suppression of the tumour suppressor proteins p53 and RbE2F. As a consequence of the elimination of these tumour suppressors, there is strong upregulation of the cellular tumour suppressor $p16^{INK4a}$ in cells infected by HPV [4–7]. This effects inhibition of the protein kinases CDK4 and CDK6 and loss of inhibition of cell cycle arrest in the G1 phase [4–7]. The loss of this "brake" that stops further proliferation is one of the most important steps in carcinogenesis.

Much less is known about carcinogenesis in non–HPV-related penile cancer. It is assumed that precursor lesions and/or chronic inflammatory stimulation leads to genetic changes that induce the inhibition of tumour suppressors, most likely $p16^{INK4A}$ (see below) [4].

2.4. Non–HPV-associated penile SCC

Overall and among the non–HPV-related penile SCCs, the usual type of SCC is the most common form. Verrucous carcinoma is an extremely well-differentiated SCC that is typically non–HPV-associated and p16-negative. Papillary carcinoma not otherwise specified (NOS) is exophytic and must be differentiated from warty (condylomatous) carcinoma and from giant condyloma. Giant condyloma, first described by Buschke and Löwenstein [5], is principally benign in that it does not metastasise, but the local growth can be infiltrating and requires surgical excision.

It is important that a pathological diagnosis of verrucous carcinoma is not applied indiscriminately to all exophytic warty penile SCCs, since the true verrucous carcinoma does not metastasise, in contrast to both papillary carcinoma NOS and warty carcinoma. An important histological criterion for the diagnosis of verrucous carcinoma is the tumour base, where tumour cells show a pushing growth pattern and not an infiltrating one. This growth pattern is typical for this entity and is maintained even in deeply infiltrating tumours, which are called the carcinoma cuniculatum subtype [4]. Owing to the important clinical implications, a diagnosis of verrucous carcinoma must be made with care.

Another well-differentiated non–HPV-associated variant of penile SCC is pseudohyperplastic carcinoma. It is typically confined to the foreskin and associated with lichen sclerosus. It can be difficult to differentiate from reactive inflammatory squamous cell hyperplasia.

2.5. HPV-associated penile SCC

Expression of p16 in tumour tissue is strongly associated with HPV positivity; p16 is therefore recognised as a surrogate marker for HPV in penile SCCs.

In this group, basaloid carcinoma is the most common. It is a poorly differentiated neoplasia, consisting of solid nests of basaloid cells, often with centrally located comedo-like necroses, and is typically p16-positive. Clinically, it is an aggressive tumour with early lymphogneic metastasis.

Warty (condylomatous) carcinoma has good prognosis and is macroscopically similar to a benign condylomata acuminatum but is microscopically distinguishable by