The Emerging Role and Promise of Biomarkers in Penile Cancer

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KEYWORDS

• Penile • Biomarkers • Prognostic • Molecular • Squamous cell carcinoma

KEY POINTS

- Penile cancer is a rare malignancy, making it difficult to extrapolate the results of many investigations in this domain.
- There is no reliable biomarker routinely available to help clinicians predict outcomes and select patients for further treatment after excision of the primary lesion.
- Knowledge of the link between human papillomavirus (HPV) and carcinogenesis of penile cancer is improving, allowing better identification of the prognostic significance of HPV.
- Other promising markers are under investigation, including plasmatic SCC and cytogenetic markers.

INTRODUCTION

Epidemiology

Penile carcinoma is a rare disease, accounting for only 1640 new cases diagnosed in the United States in 2014.[1] The incidence is higher among men in developing countries of Asia, South America, and Africa. Risk factors for penile carcinoma include chronic inflammation, lichen sclerosis, phimosis, and tobacco use[2]; one-third of cases can be attributed to human papillomavirus (HPV) infection.[3] Because of its localization, this malignancy can be a source of potentially devastating psychosexual distress, in addition to the other factors associated with malignancies.

Pathology

Penile squamous cell carcinoma (pSCC) is the most common malignant disease of the penis, accounting for more than 95% of cases of penile carcinomas. The American Joint Committee of Cancer recognizes 4 subtypes of SCC:

- Verrucous
- Papillary squamous
- Warty
- Basaloid

The verrucous subtype is known to be of low malignant potential, whereas the other types have a worse prognosis.

Management

The current guidelines of the American Urologic Association recommend a surgical amputation of the primary tumor. Prognostic factors after treating the primary lesions mainly depend on the presence of regional lymph nodes metastases (LNM), which are found in 25% of men at presentation.[4,5] Hence, establishing the lymph node status for

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each patient is relevant at baseline to determine the prognosis and, thus, the need for further treatment and following.

The biology of pSCC is such that it exhibits a prolonged locoregional phase before distant dissemination, also providing a rationale for the therapeutic value of lymphadenectomy, what has demonstrated survival benefits.[6] Yet, it has been suggested that 20% of men with pSCC have nodal metastases that are not clinically evident at the time of initial presentation.[7]

Clinical examination to determine the lymph node status is unreliable in inguinal lymph nodes; the incidence of occulted metastases varies between 2% and 66%.[8] The sensitivity and specificity of computed tomography or MRI are not sufficient as 50% of enlarged nodes show no malignancy.[9] Other methods like the PET with fludeoxyglucose 18 scanner have been suggested for nodal staging, but the results have been inconclusive. Minimally invasive techniques, such as fine-needle biopsy or sentinel node biopsy, have been used for nodal staging.[7,10] Based on recent results, dynamic sentinel lymph node biopsy (DSNB), which relies on the injection of the primary lesion with blue dye and a radioactive tracer, was shown to have a false-negative rate of 7.0% and a complication rate of 4.7%.[11] Association with fine-needle aspiration of suspicious lymph nodes can help to improve DSNB sensitivity. But these techniques require a multidisciplinary team consisting of urologists, nuclear medicine physicians, and pathologists in addition to specialized equipment and training.[12] So far, the gold standard to determine the inguinal lymph node status is inguinal lymph node resection, which is an invasive procedure associated with significant morbidity.[13] Even if the therapeutic benefits outweigh these complications for patients who have lymph node involvement, only 20% of those with clinically nonpalpable lymph nodes will harbor occult metastasis.

To select candidates for inguinal lymphadenectomy for patients with clinically negative inguinal nodes, guidelines[3] are mainly based on primary penile histology, including stage, lymphovascular invasion, and grade of primary tumor[14]; but a recent prospective study stipulates that these criteria alone are still insufficient, with many patients (82%) being subjected to unnecessary lymphadenectomy with this method of selection.[15]

These limitations to penile cancer stage provide the underpinning for the identification of more reliable penile cancer biomarkers.

Currently, there are no existing biomarkers for pSCC routinely available; but ongoing research has identified biomarkers, which can be classified into several types:

- Plasmatic biomarkers
- Proliferation associated markers
- HPV-related markers
- P53
- Cytogenetic markers

PLASMATIC BIOMARKERS

Squamous Cell Carcinoma Antigen

Squamous cell carcinoma antigen (SCCAg) is a tumor-associated glycoprotein and a member of the serine protease inhibitor family. It can be measured using a microparticle enzyme immunoassay. In cervical and anal carcinoma, SCCAg has been successfully used in both staging and following the course of the disease.[16,17]

There are few clinical studies examining the reliability of SCCAg in penile cancer.

Laniado and colleagues[18] found that SCCAg was elevated in patients with LNM and demonstrated that an elevated SCCAg level had a sensitivity of 57% and a specificity of 100% for predicting nodal metastases at the 1.50 μg/L cutoff. This same study demonstrated that SCCAg was a useful tool in following patients after excision of the primary lesion. In this study, levels of SCCAg increased exponentially in patients who subsequently developed nodal metastases and before any clinical or radiological evidence of nodal involvement.

More recently, a prospective study evaluated the clinical use of SCCAg in 16 patients with penile cancer and suggested that the sequential measurement of plasma SCCAg might indicate the presence of LNMs and/or distant metastases before they are detected clinically or by imaging, allowing early and potentially curative inguinal nodes dissections. It also demonstrated that SCCAg was useful for monitoring patients' response to treatment.[19]

In a larger series including 54 patients, Hungerhuber and colleagues[20] reported a correlation between tumor burden and SCCAg, which increased significantly with extensive lymph node involvement and metastatic disease. They also reported that SCCAg was powerful for monitoring treatment control and early detection of recurrence after treatment.

The prospective series of Zhu and colleagues,[21] based on the data of 63 patients with penile cancer, showed that despite the confirmation that SCCAg is significantly associated with nodal status, it could not accurately predict the presence of occult inguinal metastasis. These investigators further demonstrated that SCCAg was an independent prognostic factor in node positive cases and was an important predictor