

What should be done and what not in the Management of Patient with Penis Cancer: A Non-Systematic Review of the Literature

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ABSTRACT

Penis cancer is a rare condition in Europe, for whose onset phimosis and poor hygiene are strong risk factors. More than 95% of penile carcinomas are squamous cell carcinomas. Early disease is curable in most patients, who can be treated by conventional penile amputation or, in selected cases, by organ preserving techniques. For more advanced primary tumors, penile amputation is necessary. Survival of patients with penis cancer is strongly related to the presence and extent of nodal metastases, for the treatment of which inguinal lymphadenectomy is crucial. The role of chemotherapy, as adjuvant and neoadjuvant or primary treatment in metastatic disease, needs to be further explored in prospective clinical trials.

Keywords: Penis cancer; Inguinal lymphadenectomy; Adjuvant chemotherapy; Multimodal therapeutic approach

INTRODUCTION

In industrialized countries, penile cancer is a rare condition, affecting less than 1:100,000 European males [1]. In contrast, in some other parts of the world (such as South America, South East Asia and Africa) the incidence is much higher, accounting for 1%-2% of tumors in men. For example, in Uganda, it is the most commonly diagnosed male cancer [2,3]. The incidence of penile cancer increases with age [4], showing a peak in the sixth decade. However, it can occur also in younger men [5]. Penile cancer is a common finding in regions with a high prevalence of HPV, which is the hypothetical reason for the worldwide variation in incidence of this type of cancer [6]. Penile cancer (PC) is not associated with HIV or AIDS. Penile carcinoma is usually a Squamous Cell Cancer (SCC), although there are several subtypes of penile SCC with different clinical features and natural history (Table 1). Penile SCC usually arises from the epithelium of the inner prepuce or the glans. Traditionally, aggressive and radical surgery is necessary to achieve satisfactory oncological results in the treatment of penis cancer, however resulting in a high morbidity rate not only from a clinical point of view but also from a psychological aspect. Nevertheless, owing to the rapid advancement in diagnostic and therapeutic

strategies, the treatment for PC is changing. This is not surprising if we consider that penile cancer represents one of the few cancers for which the TNM (Tumour, Node, and Metastasis) staging criteria have changes multiple times in recent years, with the eighth edition currently being the last [7]. This is a nonsystematic review, based on Pubmed literature search for article containing the terms “penile cancer” and “carcinoma of the penis”, Which outlines the surgical and medical strategies in treatment of this rare condition, discussing every point of controversy.

Subtypes of penile cancer

Common Squamous Cell Carcinoma (SCC)

Basaloid carcinoma

Warty carcinoma

Verrucous carcinoma

Papillary carcinoma

Sarcomatoid carcinoma

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Mixed carcinoma
Pseudohyperplastic carcinoma
Carcinoma cuniculatum
Pseudoglandular carcinoma
Warty-basaloid carcinoma
Adenosquamous carcinoma
Mucoepidermoid carcinoma
Clear cell variant of penile carcinoma

Table 1: Hystological subtypes of penis cancer.

DIAGNOSIS OF PRE-MALIGNANT LESIONS AND PENILE CANCER

Although the awareness of and access to information about PC are still poor, therefore resulting in late presentation and worse prognosis, the detection rate of PC and pre-malignant lesions (the so-called penile intraepithelial neoplasia or PeIN) is increasing for three reasons [8]. First, there are more biopsies of the penis being carried out not only by urologists but also by dermatologists. These biopsies, often performed at the same time as circumcision for bothersome phimosis, can be performed under local anesthesia, without any risk even in patients with multiple comorbidities. Second, an increased public awareness, along with a generational change in attitudes, has led to more men presenting to a doctor for conditions affecting the genitalia. A culture shift has made it more acceptable for men to self-examine and present early to a healthcare professional. Finally, the association between Human Papilloma Virus (HPV) and cervical cancer well established in several studies and the increased trend in many countries to vaccination programs for women before exposure to sexual activity has prompted more and more authors to investigate the role of HPV infection on the onset and development of penile cancer [9]. However, among several risk factors identified for penile cancer, human papilloma virus infection plays a weak role in the onset and development of this type of tumor, being a cofactor in the carcinogenesis of only some variants of penile SCC, while others are not related to HPV (Table 2). The commonest HPV subtypes in penile cancer are types 16 and 18 [10]. For this reason, at present, except for a few countries, HPV vaccination is not generally recommended in male population. For a purely classification purpose, the penile lesions are divide in HPV-related and non HPV-related (Table 3). Unlike HPV infection, phimosis is strongly associated with invasive penile cancer [11-14], due to associated chronic infection. Then, the treatment of phimosis is important if we consider that a penile cancer may be hidden under a phimosis [15]. Likewise, the incidence of lichen sclerosus is relatively high in penile cancer. How should the clinician behave in the presence of these lesions? Any doubtful penile lesion should be biopsied and, even in clinically obvious cases, histological verification is necessary

before local treatment. Prior to definitive surgical treatment, an excisional biopsy can be performed to obtain an histological confirmation to guide further surgical and medical approaches. The size of a biopsy is not negligible if we consider that, in one study, the depth of invasion was assessed with difficulty in biopsies with an average size of 0,1 cm [16]. A punch biopsy may be sufficient when the lesion is superficial but an excisional biopsy is deep enough to correctly assess the degree of invasion and stage, making it preferable for this reason.

Risk factors

Phimosis

Chronic penile inflammation (balanoposthritis related to phimosis), lichen sclerosus

Sporalene and ultraviolet A phototherapy for various dermatological conditions such as psoriasis

Smoking

HPV infection,condylomata acuminata

Rural areas,low socio-economic status, unmarried

Multiple sexual partners. early age of first intercourse

Table 2: Aetiological risk factors for penis cancer.

Non HPV related	HPV related
SCC usual type	Basaloid SCC
Pseudohyperplastic carcinoma	Papillary basaloid carcinoma
Pseudoglandular carcinoma	Warty carcinoma
Verrucous carcinoma	Warty-basaloid carcinoma
Carcinoma cuniculatum	Clear-cell carcinoma
Papillary carcinoma	Lymphoepithelioma-like carcinoma
Adenosquamous carcinoma	
sarcomatoid carcinoma	

Table 3: Classification of penile cancers.

DISCUSSION

Management of primary lesion

Local treatment modalities for small and localised penile cancer include excisional surgery, topical chemotherapy with Imiquimod or 5-Fluorouracil (5-FU), and External Beam Radiotherapy (EBRT), brachytherapy and laser ablation. Patients should be counselled about all relevant treatment options. The treatment of the primary tumor must completely remove the penile carcinoma with as much organ preservation as possible, without compromising oncological control. In effect, because the local recurrence has little influence on long-term survival, organ preservation strategies are justified [17]. Penile preservation appears to be superior in functional and cosmetic outcomes to partial or total penectomy and, for this reason; it is considered the primary treatment method for localised penile cancer. Then, when a surgical treatment is performed, it must

guarantee negative surgical margins, which may be confirmed by intra-operative frozen section [18]. Only 3 mm of tumor-free tissue is sufficient to consider the surgical margins as negative [19]. Penile cancer can be cured in over 80% of cases if diagnosed early, but is a life-threatening disease when lymphatic metastasis occurs. While the glans resurfacing (total or partial) can be a primary treatment for PeIN or a secondary option in case of failure of topical chemotherapy or laser therapy, the latter treatment modalities are not advisable for small lesions confined to the glans, considering the need to recognize the risk of more invasive disease. External beam radiotherapy or brachytherapy are radiotherapeutic options but penis cancer in T1-T2 stage should be treated by organ-sparing surgery, with partial or total glansectomy playing a fundamental role. A “radical circumcision” is an option when the tumor is confined to the foreskin. So, in the light of the above, we can conclude that in case of penile lesions in T1/T2 stage treatment choice depends on tumor size, histology, stage and grade, site (especially relative to the meatus) and patient preference. In the case of such lesions, a question that plagues urologists is whether to perform or not intraoperative frozen sections to assess surgical margins. According to a multi-centre study, the probability to find differentiated penile intraepithelial neoplasia, squamous hyperplasia and lichen sclerosis at the surgical margins is high but this frequent finding is not relevant for cancer-specific survival [20]. For a general recommendation, 3-5 mm can be considered a safe maximum [21,22]. A grade-based on the differentiated approach can also be used, including 3 mm for grade one, 5 mm for grade two and 8 mm for grade three. This approach has its limitations due to the difficulties with penile cancer grading. For T1 and T2 disease the question is the following: organ-sparing surgery or amputation? On one hand, a conservative, organ-sparing treatment improves the Quality of Life (QoL). On other hand, local recurrence is more likely when organ-sparing approach is performed than after amputation surgery. In effect, according to one study, the local recurrence rate after organ-sparing surgery and amputation surgery (partial or radical) was 18% and 4%, respectively [23]. A largest cohort of penile surgery didn't show significant difference in survival between the organ-sparing and the amputation groups [24]. So, according to these results, although the local recurrence rates after penile-sparing surgery are higher than with penectomy (partial or radical), the survival appears to be unaffected. In case of invasive penile cancer confined to the glans with or without urethral involvement (T2), the treatment is based on total glansectomy, with or without resurfacing of the corporeal heads [25]. Radiotherapy can be an alternative while partial amputation is to perform in patients affected by penile cancer when reconstructive surgery is not possible [26]. When the penis cancer invades the corpora cavernosa and/or urethra (T3), glansectomy (with distal corporectomy and reconstruction) or partial amputation (with reconstruction) are the gold standard treatment [21,22], with a limited space for the radiotherapy. Finally, the treatment of locally advanced disease invading adjacent structures (T4) includes extensive partial amputation or total penectomy with perineal urethrostomy [22].

Management of lymph node status

In the treatment of penis cancer, the management of regional lymph nodes plays an important role. The inguinal lymph nodes, followed by the pelvic lymph nodes, provide the regional drainage system of penis. The superficial and deep inguinal lymph nodes are the first regional nodes to be affected, which can be uni- or bilateral [27]. Pelvic nodal disease does not occur without ipsilateral inguinal lymph node metastasis. Also, crossover metastatic spread, from one groin to the contralateral pelvis, has never been reported. Further lymphatic spread from the pelvic nodes to retroperitoneal nodes (para-aortic, para-caval) is classified as systemic metastatic disease. The management of regional lymph nodes is decisive for patient survival and the cure can be achieved only when the lymph node disease is confined to the regional lymph nodes. In this case, radical lymphadenectomy is the treatment of choice but multimodal approach, based on surgery and chemotherapy, is often indicated. The clinical inguinal lymph node status can show three possible scenarios, on which the future therapeutic choice depends. First, when the patient shows clinically normal inguinal lymph nodes (cN0), surveillance, invasive nodal staging or radical lymphadenectomy represent the therapeutic modalities. Surveillance is only recommended in patients with pTis/pTa tumors and with the appropriate caution in low risk G1 pT1 tumours [28-30] but it is necessary that the patient enrolled in surveillance program is informed about the risk of regional recurrence arising later from existing micro-metastatic disease. Then, such a treatment modality deprives the patient of the advantages of an early surgical approach. In effect, when the long-term survival is assessed in clinically node-negative patients, an early inguinal surgery is better than to later lymphadenectomy with regional nodal recurrence [31,32]. These results are in agreement with those of one prospective study which compared the five-year overall survival (OS) between bilateral lymphadenectomy, radiotherapy and surveillance in these patients (74% vs. 66% and 63%, respectively) [33]. Whereas there are no imaging techniques which can detect micro-metastatic disease, invasive lymph node staging is indicated for pT1 tumors of intermediate and high risk, as well as for T2-T4 tumors [32,34]. This staging cannot be performed by fine-needle aspiration cytology but by either Dynamic Sentinel-Node Biopsy (DSNB) or by modified Inguinal Lymphadenectomy (mILND), both of which are standard techniques [35]. If lymph node metastasis is found, ipsilateral radical inguinal lymphadenectomy is indicated. Secondly, when the patient shows uni- or bilateral palpable inguinal lymph nodes (cN1/cN2), metastatic lymph node disease is highly likely. For this reason, an antibiotic therapy (supported by the belief that the increased volume of the lymph nodes is of an inflammatory nature) not only constitutes a diagnostic and therapeutic mistake but also a strong negative prognostic impact, delaying a curative surgical treatment. Therefore, palpably enlarged groin lymph nodes should be surgically removed, pathologically assessed (by frozen section) and, if positive, a radical inguinal lymphadenectomy should be performed. Owing to impaired lymph drainage from the legs and scrotum, radical inguinal lymphadenectomy is associated with a significant morbidity, which can be as high as 50% when the patient shows

risk factor such as increased body mass index (BMI) [36]. However, radical inguinal lymphadenectomy is life-saving treatment and, for this reason, the fear of associated morbidity must not represent an obstacle to the execution of this therapeutic procedure [37]. In this regard, the role of minimally-invasive surgical techniques (laparoscopic, robot-assisted) for inguinal lymphadenectomy should be evaluated in large series, considering that small series have reported a significantly reduced post-operative morbidity, except for the rate of lymphoceles, when a minimally-invasive surgery is performed [38-42]. However, given the low frequency of penile cancer and the heterogeneity of the clinical presentation, it is difficult to conduct studies with a large population sample. When two or more inguinal lymph node metastases on one side and/or extracapsular lymph node extension are present, ipsilateral pelvic lymphadenectomy is necessary.

In effect, one study reported a 23% pelvic lymph node positivity rate when more than two inguinal nodes are positive, increasing to 56% in patients with more than three positive inguinal nodes or extracapsular extension [22,43]. Positive pelvic nodes lead to a worse prognosis than only inguinal nodal metastasis (five-year Cancer Specific Survival [CSS] 71.0% vs. 33.2%). According to a study which assessed 142 groin node-positive patients, significant risk factors for pelvic nodal metastasis are the number of positive inguinal nodes (cut-off three), the diameter of inguinal metastatic nodes (cut-off 30 mm) and extra-nodal extension. The percentage of pelvic nodal metastases was 0% without any of these risk factors, increasing to 57,1% when all three risk factors are present [44]. Pelvic lymphadenectomy may be performed simultaneously with inguinal lymphadenectomy or as a secondary procedure. If bilateral pelvic dissection is indicated, it can be performed through a midline suprapubic extraperitoneal incision. It is important to avoid unnecessary delay if these procedures are indicated [45]. In patients with pN2/pN3 disease, adjuvant chemotherapy is recommended after lymphadenectomy, considering that a retrospective study reported a better long-term disease free survival DFS when adjuvant chemotherapy is performed after radical lymphadenectomy (84% with adjuvant chemotherapy vs. 39% without it) [46]. These results are similar to those of more recent studies [47-49]. The therapeutic program in patients with large and bulky, sometimes ulcerated, inguinal lymph nodes is based on the results of staging by thoracic, abdominal and pelvic CT scan. In effect, showing a poor prognosis, these patients are suitable for multimodal therapeutic approach based on neoadjuvant chemotherapy which is followed by radical lymphadenectomy in responders [50-52], with a long-term survival obtained only in 37% of cases [50]. These results are similar to those of contemporary studies [53,54].

The role of radiotherapy in the treatment of penis cancer

The use of radiotherapy for the treatment of inguinal lymph node is not evidence-based because it doesn't improve oncological outcome, especially when compared to inguinal

radical lymphadenectomy [55,56]. A comparative retrospective study showed that adjuvant chemotherapy was far superior to adjuvant radiotherapy after radical inguinal lymphadenectomy in node-positive patients [46]. In addition, a large retrospective analysis of the SEER database (National Cancer Institute Surveillance, Epidemiology and End Results Program) of 2,458 penile cancer patients treated with either surgery alone or surgery plus External Beam Radiation Therapy (EBRT) concluded that the addition of adjuvant EBRT "had neither a harmful nor a beneficial effect on CSS" [57]. For all these reasons, the role of radiotherapy is limited to advanced lymph node disease, representing a palliative option.

CONCLUSION

This article describes the correct methods of intervention in the diagnosis and management of the PC, discussing controversial points. Increased knowledge and research allows men with CP to achieve better functional and oncological outcomes.

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