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Organ-sparing Treatment for Penile Cancer

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Abstract

Penile cancer is a rare urological malignancy. Diagnosis may be delayed, leading to more radical surgery and higher physical and psychological morbidity. In the last decade there has been a trend towards the use of penile-sparing surgery. We describe the contemporary role of organ-sparing techniques in the management of primary squamous cell carcinoma of the penis. In particular, we report on the oncological and functional outcomes described in the literature.

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1. Introduction

Penile cancer is a rare genitourinary cancer, with an incidence of 1 in 100 000 in Western countries and accounting for 1% of all male malignancies [1]. A number of predisposing factors have been identified, including exposure to human papilloma virus (types 16, 18, 31, and 33), phimosis, chronic inflammatory conditions including balanoposthitis and lichen sclerosis, and smoking [2].

The management and prognosis of this cancer are highly dependent on tumour, grade, and stage, including the involvement of regional lymph nodes. Unfortunately, many patients present to clinical services late with advanced disease and are subsequently subject to more radical surgery with its associated physical, psychological, and sexual morbidity.

Some of the earliest reports on the treatment of penile cancer involved extremely disfiguring surgery in which all parts of the scrotum, crura, and penile shaft were removed, leaving patients with a penile urethrostomy. While often providing good oncological control, the subsequent disfigurement and functional consequences for the patient cannot be underestimated.

Although penile cancers are rare, the tumour biology is well understood. While many histological subtypes exist, >95% of tumours are squamous cell carcinoma (SCC) [1]. There are many forms of SCC, including the warty basaloid form (50–60% of mixed penile SCC), usual verrucous, usual warty, usual basaloid, and usual papillary, as well as other rarer combinations [1]. The differential diagnosis includes other malignant lesions such as melanomas, mesenchymal tumours, lymphomas, and distant metastases, typically from prostate or colorectal cancers (adenocarcinomas).

Historically, management strategies have traditionally mirrored those for other tumours that originate from squamous cells, most notably skin and breast cancer. These tumours are usually excised with wide margins of 2–3 cm. Consequently, to achieve this level of clearance for penile cancer, patients have undergone surgery in the form of partial or radial penectomy.

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Ensuring adequate oncological control is naturally the most important outcome for many patients and clinicians. However, the traditional paradigms are being challenged as our understanding of the disease grows, surgical techniques become more refined, and greater emphasis is placed on patient preference and their assessment of a "good outcome" rather than strictly clinical parameters. A more balanced approach has especially been advocated in the management of tumours for which patients are left with severe physical disfigurement, functional compromise, or psychological distress. In penile cancer, areas of specific concern for patients include preservation of penile length and appearance, sexual function, and normal voiding.

In 2000, Agrawal et al [3] carried out a review of 64 patients who had undergone partial or total penectomy for penile cancer. Specimens were evaluated in 5-mm sections to assess for microscopic spread beyond the visible tumour. Patients included in the study had disease of all T stages and grades. The majority of tumours had either none or <5 mm of microscopic extension beyond the visible edge of the lesion. Two of the 12 grade 3 lesions were positive histologically at 10 mm, but none of the tumours extended up to or beyond 15 mm [3]. This was one of the first publications to challenge the traditional surgical margins.

This work has been further substantiated by Minhas et al [4] in a retrospective review of 51 men with penile SCC managed with wide local excision, glans resection, or partial penectomy. Three patients had a positive margin that was managed surgically, and two developed local recurrence requiring partial penectomy [4]. The group concluded from this study that a 2-cm margin was excessive and that taking more conservative resection margins still offered excellent oncological control.

The same group subsequently published further data on 179 patients who were followed-up for an average of 42.8 mo. The mean distance from the excision margin was 5.78 mm. Twelve patients (6.7%) had involved margins but all were treated with further penile-preserving surgery (PPS) and subsequently had negative margins at completion surgery. However, 16 patients developed local recurrence at 5 yr [5]. To further support this paradigm shift, a recent paper by Parnham et al [6] evaluating glansectomy reported a retrospective histological analysis that revealed that resection margins of <5 or 10 mm showed no local recurrences following surgery.

These papers have demonstrated that the traditional margins of 2 cm, which were rather arbitrary and based on minimal evidence or were specific to other cancers, can be challenged without compromising patient outcome. Furthermore, as we explore in detail later, local recurrence has little effect on long-term survival, thus making such organ-preserving strategies safe. This change has been reflected in the latest European Association of Urology (EAU) guidelines, which state that a margin of 5 mm offers appropriate oncological control [1].

In this review, we discuss a variety of penile-preserving options for the management of premalignant penile lesions and penile tumours, their indications, and the current data on outcomes.

2. Penile-preserving techniques

The treatment aim for primary penile cancer is to remove the tumour completely and ensure oncological control while preserving penile length and function. It is imperative that a histological diagnosis is confirmed and local staging is performed for all patients. In the UK, penile cancer management has been centralised to high-volume specialist referral centres. Clinical and radiological staging may involve the use of computed tomography (CT) and/or magnetic resonance imaging (MRI) to evaluate the depth of invasion and locoregional spread. Table 1 lists the various treatment modalities currently used according to histological staging of the disease.

2.1. *Non-surgical techniques*

2.1.1. *Topical agents*

Topical agents have typically been used for the treatment of small or premalignant lesions such as penile intraepithelial neoplasia (PeIN), erythroplasia of Queyrat (EQ), Bowen's disease, and lesions involving the prepuce or the glans. The most common agents used are immunomodulatory agents, such as imiquimod, and 5-flurouracil (5-FU), an antimetabolite [1]. Imiquimod enhances both innate and cell-mediated immune pathways, stimulating cytokine release. Antigen-presenting and Langerhans cells are also activated, promoting their migration to regional lymph nodes. This topical agent was initially approved in the USA in 1997 as a treatment for anogenital warts, but after further clinical studies were conducted, the treatment is now used for a wide variety of cutaneous tumours [7]. 5-FU acts as an antimetabolite and prevents cell proliferation by inhibiting the enzyme thymidylate synthase and blocking the thymidine formation required for DNA synthesis [8].

There is no specific treatment regimen described for these agents, but typically they are applied either once or twice a day for a period of 3–6 wk [9]. The use of topical agents is advantageous for many reasons. They have a relatively low cost, can be delivered via ambulatory care to patients, and have a limited side-effect profile. The treatments can also be used in patients who have had a positive margin following circumcision.

However, the agents can alter the appearance of the glans, making it unsightly and subject to difficulties in post-treatment clinical interpretation, potentially leading to recurrences being missed. This could possibly lead to delayed subsequent treatment. Patients often report irritation, soreness, and erythema, and in some cases can develop severe allergic or hypersensitivity reactions.

The efficacy of these agents is rather mixed and limited, with the majority being gathered from very small case series often consisting of only two or three patients [10–12].

One of the first reports was by Goette and Carson [13], who treated seven patients with PeIN using 5-FU. All patients had a post-treatment biopsy that revealed normal histological findings and a recurrence-free follow-up period of up to 70 mo. Bargman and Hochman [14] presented data for 24 patients with 26 biopsy-confirmed PeIN treated with