Primary penile cancer organ sparing treatment

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Introduction  
Surgical treatment of penile cancer is usually associated with mutilation; alterations in self-esteem and body image; affecting sexual and urinary functions; and declined health-related quality of life. Recently, organ sparing treatment has appeared and led to limiting these complications.

Material and methods  
An extensive review of the literature concerning penile-preserving strategies was conducted. The focus was put on indications, general principles of management, surgical options and reconstructive techniques, the most common complications, as well as functional and oncological outcomes.

Results  
Analyzed methods, e.g.: topical chemotherapy, laser ablation therapy, radiotherapy, Moh’s microscopic surgery, circumcision, wide local excision, glans resurfacing and glansectomy are indicated in low-stage tumors (Tis, Ta-T2). After glansectomy, reconstruction is also possible.

Conclusions  
Organ sparing techniques may achieve good anatomical, functional, and psychological outcomes without compromising local cancer control, which depends on early diagnosis and treatment. Penile sparing strategies are acceptable treatment approaches in selected patients with low-stage penile cancer after establishing disease-risk and should be considered in this population.

Key Words: penile cancer ›› organ sparing treatment ›› QoL

INTRODUCTION

Penile cancer is an uncommon malignancy in Europe and North America with a reported incidence of 0.1 to 0.9 per 100 000 men [1, 2]. However, in developing countries the incidence is higher and reaches 50 per 100 000 men in north-eastern Brazilian states [3]. This various worldwide distribution depends on age, circumcision practice, hygiene patterns and risk factors for penile cancer [2, 4]. Phimosis, human papillomavirus infection, chronic inflammatory conditions (balanoposthitis and balanitis xerotica obliterans), sexual history (multiple partners, early age at first intercourse), and treatment with psoralen and ultraviolet A phototherapy are strongly associated with risk of developing penile cancer [5–8].

The surgical management of penile cancer depends on the stage of the disease, TNM (tumor nodus tumor metastases) staging system, as well as the grade and lesion location, which is detailed in Table 1. The mainstay of surgical treatment relies upon wide excision including partial penectomy and total penectomy. More recently, a variety of operative techniques and therapeutic strategies have been developed to reconcile good functional and psychological outcomes with sufficient oncological control through organ sparing techniques [9, 10]. While large retrospective studies report a statistically higher local recurrence rate following organ-sparing techniques compared with penis amputation, repeat organ sparing resection for local recurrence appears to provide satisfactory outcomes which results in corresponding overall survival rates after
preserving and radical treatment [10]. Penile amputation frequently results in unsatisfactory side effects of penile disfigurement or emasculation along with effects on corporal image, self-esteem and genital sensibility, frequently impairing sexual function or micturition. As a result, it is understandable why patients are afraid of the mutilating effects after total penectomy and are unwilling to undergo radical treatment [11]. Patients’ preferences should be respected in the treatment decision-making process and psychological support should be provided while maintaining oncological outcomes. The aim of this article is to provide a contemporary review of the penile–sparing approaches in the management of primary penile cancer. Emphasis is placed on indications for appropriate stages, general principles of management, surgical options and reconstructive techniques, as well as functional and oncological outcomes.

**Topical chemotherapy**

Agents used for topical chemotherapy or immunotherapy of penile cancer are 5-fluorouracil (5-FU) 5%, imiquimod 5% and interferon alfa-2a creams [11]. Indications for this treatment are premalignant and superficial lesions, such as carcinoma in situ (Erythroplasia of Queyrat, Bowen’s disease) and Bowenoid papulosis. 5-FU is frequently administered as a first line therapy [12, 13, 14]. There is no specific regimen for 5-FU therapy. The most common method is applying the medication directly onto the lesion for a 12-hour duration every other day for 4–6 weeks [11, 14, 15], while other schemes suggest applying the cream twice daily for 3 weeks [13]. If necessary, the cycle can be repeated. As a second-line treatment, imiquimod 5% can be applied in a similar manner [4], although there are some reports of successful use as a first-line therapy [14, 16]. Toxicity and adverse events are relatively low. The most common side effects of topical chemotherapy include discomfort, erythema, irritation and soreness. Hypersensitivity or allergy to 5-FU are also possible and it can manifest as a severe allergic reaction—generalized dermatitis [15]. 5-FU has demonstrated good oncological outcome without evidence of recurrence in post treatment biopsy after a 5 year follow-up [17]. A larger retrospective study concerning the treatment of penile CIS with 5-FU as a first- and imiquimod as a second-line therapy, report complete response in 57% and partial response in 13.6% of patients [12].

**Laser ablation therapy**

Laser ablation of the superficial primary tumor offers a penile preservation strategy. Indications for treatment include in situ disease and, in some publications, also T1 tumors [11]. Contraindications are lesions with >6 mm depth invasion and T2 tumors [18]. The types of lasers which are most commonly used in clinical practice are the CO₂ laser and the neodymium-yttrium-aluminium-garnet (Nd:YAG) laser. These lasers differ from each other in wavelength, which is 10.6 μm for the CO₂ laser and 1.06 μm for the Nd:YAG laser [2, 15]. This is reflected in tissue penetration depth: 0.1 mm for CO₂ laser and 4.2 mm for Nd:YAG [11]. Because of its low penetration power, the CO₂ laser is an alternative to topical chemotherapy as a first-line treatment of penile cancer in situ [12]. The mechanism of tissue destruction differs between the two types of lasers. The CO₂ laser ablation leads to tissue carbonization and vaporization, while Nd:YAG causes protein denaturation, coagulative necrosis and also limited carbonization and vaporization [15]. When managing penile carcinoma with laser treatment, it is imperative to ablate the surrounding area of the tumor bed. A margin of 8–10 mm extending beyond the tumor site should be treated when using the CO₂ laser [19]. Usage of Nd:YAG laser requires a minimum 3 mm rim around the primary lesion ablation site [20, 21]. Peniscopy, microscopic examination of the penis with a colposcope after application of 5% acetic acid, can be helpful to detect lesions suspected of malignancy [22]. Complications after CO₂ laser treatment, which include bleeding and meatal stenosis, are rare, occurring in less than 1%. In one study, there were no urinary or sexual function complica-

| **Table 1. Conservative and organ sparing treatment options for penile cancer [8]** |
|-----------------|---------------------------------------------------------------|
| **Primary tumor** | **Conservative or organ sparing treatment** |
| Tis             | Topical chemotherapy, laser, WLE, glans resurfacing |
| Ta, T1a         | Laser with/without circumcision, WLE with/without circumcision, glans resurfacing, glansectomy (partial), radiotherapy for lesion <4 cm |
| T1b and T2 confined to the glans | WLE with reconstructive surgery, Laser with circumcision, glansectomy, radiotherapy for lesion <4 cm |
| T2 with invasion of the corpora cavernosa | Partial penectomy and reconstruction, radiotherapy for lesion <4 cm |
| T3 with invasion of the urethra | No recommendation for organ sparing surgery |
| T4 with invasion of other adjacent structures | no recommendation for conservative treatment or organ sparing surgery |
| Local recurrence after conservative treatment | Salvage surgery with penis-sparing treatment in small recurrences or partial amputation |
|                  | Large or high-stage recurrence: partial or total amputation |

WLE – wide local excision
tions observed after Nd:YAG laser application [8]. Recurrence of penile cancer after CO₂ laser ablation occurs in 10–26% of patients [13]. Results of Nd:YAG laser treatment depends on tumor stage with recurrence rates ranging from 3.1% to 48% [18, 20].

Mohs microscopic surgery

The Mohs microscopic surgical technique was developed in the 1930’s for treatment of common skin cancers. Although mohs microscopic surgery (MMS) has been adopted for the treatment of penile cancer, few studies using the management option have been reported to date. During MMS, the tumor is excised in horizontal layers with concomitant multiple frozen sections and microscopic evaluation until the surgical bed is cancer free. This microscopic guidance allows for the removal of tumor tissue within clear resection margins and the preservation of uninvolved penile tissue for good cosmetic and functional results. According to Frederic Moh’s data, this technique is very much stage-dependent, successful mainly in small (<1.0 cm) low stage, low grade lesions [23]. Tumor size has been shown to be an important predictor for local control with no recurrence in small lesions, <2 cm, and 50% recurrence with lesions >3 cm. In other series, overall recurrence rates were 32% after the first MMS procedure, apparently higher than after amputations; however, in those cases patients were suitable for further Mohs procedures [24]. Although complications are rare, metatal stenosis and organ disfigurement are reported, the latter mostly in larger high stage tumors. While attractive because of negative margins reassurance and preservation of penile anatomy and function, careful patient selection for this technique remains crucial for treatment success. MMS may be offered to men with CIS or distal superficially invasive tumors who desire penile preservation for the best outcomes.

MMS has gained limited popularity among urologists as it is time consuming and requires a multidisciplinary team with close cooperation between urologist and pathologist.

Circumcisions

The majority of patients with penile cancer are uncircumcised. About 20% of new malignancies involve only the prepuce at presentation. In these cases, circumcision may be sufficient for curative treatment. Specifically, circumcision maybe be an acceptable treatment modality for lesions limited to distal prepuce that are low stage (Tis, Ta, T1) and low grade (G1,G2) [2, 25, 26]. When the tumor involves the basal prepuce, excision needs to be extended to the penile shaft to ensure negative surgical margins [27]. However, this simple procedure is related with poor local control and recurrence rates as high as 50% have been reported [2, 26]. Therefore, careful selection and close follow-up of patients is mandatory.

Wide local excision

Recent growing data on the oncological safety of negative surgical margins of only a few millimetres have encouraged urologists to perform local excision of penile carcinoma in select cases [28–31]. Wide local excision (WLE) is an approved local treatment modality for glans tumors of up to T2 and low stage and grade tumors of the shaft (up to T1 G2) [8]. In small lesions, primary closure of the wound is often possible. However, closing larger lesions may result in penile disfigurement or tilting, affecting micturition and erectile appearance. Consequently, in such cases grafting may be required, preferably with split thickness skin grafts. There are no strict limitations in the terms of lesion size for this management technique, but rather it is considered individually depending on the glans size or tumor location. Tumors covering more than half of the glans; close to the urethral meatus; urethral involvement; and concurrent CIS are contraindications for WLE. Local recurrence is not uncommon with the 5 year recurrence-free survival for T1 and T2 tumors being 63% [32]. Although local control is achieved in most cases with WLE, close follow up is required to monitor for recurrence which could signify regional lymph node spread and affect the patient’s prognosis. WLE is associated with less postoperative complications and leads to better sexual outcomes as comparing to glansectomy, which is often an alternative. Some authors consider WLE the best approach for treating primary penile tumors when feasible [33].

Glans resurfacing

Glans resurfacing is a relatively new procedure that was first described in 2000 by Depasquale and colleagues for the treatment of extensive balanitis xerotica obliterans and subsequently adapted for superficial glans cancers [34]. It is an acceptable treatment modality for Tis, Ta and T1a disease. Literature supports its use for extensive pre-malignant lesions and carcinoma in situ, where it can be performed as a primary procedure or when treatment with topical agents fails [15, 35, 36]. This procedure is performed under tourniquet control. After marking the glans quadrants, epithelium and subepithelial tissue is removed from the
spongiosum by sharp dissection, starting from the meatal edge and proceeding to the coronal sulcus and slightly over to the shaft skin (Figure 1). Next, the resection site is covered, typically with a split-skin graft (SSG) harvested from the lateral thigh, or alternatively with tunica vaginalis or buccal mucosa. The graft is trimmed to size and then carefully sutured with interrupted absorbable sutures to meatal and shaft edges (Figure 2). Quilting sutures are placed in a regular fashion to ensure graft adherence, occasionally complemented by small longitudinal incisions. After completion of the surgery a catheter is placed and compressive dressing is applied. Patients remain on bed-rest for usually 3–5 days, after which the catheter and bandage are removed and patients are discharged home. After 4–6 weeks the cosmetic outcome is usually excellent. In several studies no complications were reported, but there is a potential risk of graft loss and need for re-grafting [15].

In cases where lesions affect part of the glans (less than 50%), partial glans resurfacing is an option. The technique is analogous to total glans resurfacing, where a wedge excision of the tumor is performed. In these cases, peniscopy done prior to surgery may be helpful in assessing lesion occurrence and for better resection planning [37]. Shabbir et al. reported high positive margins rates of 28% for this technique with the need for further conservative treatment [35]. Other studies have used glans resurfacing for premalignant lesions with excellent results [15, 38]. However, patients should be informed of the risk of positive margins and need for secondary treatment. Overall recurrence rates at mid-term follow-ups were no higher than 6% [35] with no cases of local failure in other studies [15].

Glansectomy

Since penile cancer can occur in up to 80% of cases distally, either on the glans or prepuce, the majority of patients may be amenable to glansectomy [2, 39] which was first described by Austoni in 1996 [27]. Glansectomy is a treatment modality for glandular tumors Ta, T1 and T2 [26, 30]. Either total or partial glansectomy may be performed depending on cases, both with or without grafting.

Total glansectomy starts with catheter insertion and a tourniquet is placed at the penile base for bleeding control. A circular subcoronal incision is made down to the Buck’s fascia. At this point a plane is developed in which the glans is separated from the corpora cavernosa (Figure 3). Neurovascular bundles are sectioned and the urethra is divided, freeing it from the specimen. Next the urethra is ventrally spatulated and a new meatus is formed by fixing
it to the corpora cavernosa (Figure 4). Before the glans reconstruction, sections of tunica albuginea and distal urethral margin must be taken for intraoperative microscopic assessment. The neoglans is usually formed from SSG in a fashion similar to the one described for glans resurfacing, covering the corporal tips (Figures 5 and 6). The penis may be also reconstructed without grafting, as in a 'parachute technique', where corporal tips are covered with sectioned shaft [40]. Efforts have been made to further improve reconstructive surgery for better outcomes. Depasquale's technique of cavernous rotation in which the extremities of corpora are separated and rotated ventrally and then sutured under the urethra to imitate the appearance of the glans and coronal sulcus was used in one series with good cosmetic and functional results, yet with considerably high complications rate of 27% [34]. Since reduction of penile sensitivity seems to be a major functional problem after grafting, neoglans formation by everting the spatulated urethra was also tried to avoid this side effect [36, 41]. For smaller lesions located distally near the urethral meatus and up to stage T1a, partial glansectomy may be performed. Reconstruction with our without grafting is possible, the latter through penile shaft skin coverage or using a preputial flap [27, 42]. Local recurrence rate for glansectomy has been reported to be 8% in long-term follow-up, and 9% for inguinal nodes metastases [40]. Potential complications for this method are graft loss, meatal stenosis and urine spraying. As to functional outcomes, it is connected with decreased penile length and reduced sensibility and may therefore negatively affect sexual satisfaction [33].

**Partial penectomy with glans reconstruction**

If tunica albuginea or early corporal involvement occurs, traditionally it would be treated with partial penectomy for the best oncological outcomes [8]. Alternatively, in patients who are adamant about penile preservation, distal corporectomy with reconstruction of the corporal heads and grafting may be performed [43]. The corpora cavernosa are sutured and a neoglans is reconstructed. The neoglans gets covered by a split-skin graft.

**Radiotherapy**

Radiation therapy is an option in the management of penile cancer, stages CIS-T3 [8]. There is a need for two forms of radiation therapy in the treatment of penile carcinoma: external-beam radiotherapy (EBRT) or brachytherapy (BT). Indications for EBRT include superficial or exophytic lesions of <4 cm,
and tumour location on the glans or coronal sulcus. A tumor <4 cm on the glans penis with <1 cm of invasion may be treated with BT [44, 45]. Contraindications for EBRT or BT include any penile tumor >4 cm with concurrent inguinal lymphadenopathy [11]. Typically, EBRT is administered in 2 Gy fractions per day. The treatment schedule consists of five fractions per week for a duration of 6–7 weeks. A total provided dose is 66–70 Gy. Two differing BT techniques have been employed in the treatment of penile cancer. The first technique involves a radioactive mold placed over the penis. The second technique is the implantation of a radioactive seed (Ir 192) which delivers a predetermined dose to the penile tissue. In order to reduce radiation-induced complications, circumcision should be performed prior to radiotherapy [11]. Penile brachytherapy usually delivers a total dose of 55–60 Gy over 4–5 days. Local recurrence occurs in 10–40% of cases [44, 46]. The 5-year rate of penile preservation after BT ranges from 70% to 88%, which is higher than the corresponding 36–66% rates for EBRT [47]. Complications after radiotherapy include urethral adhesions with a deviated stream; urethral strictures; meatal stenosis; fibrosis; pigmentation; and radiation-induced penile ulceration or necrosis [11, 48].

CONCLUSIONS

Penile sparing procedures are acceptable management options in the select risk-informed patient after establishing disease-risk variables. Candidates for penile-sparing procedures must undergo close surveillance and be adherent to follow-up requirements which allows early detection of local recurrences. Disease recurrence mandates prompt and effective salvage procedures.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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