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RESEARCH ARTICLE

Evolving Perspectives in Penile Cancer Management: How to Retain Functional Outcomes

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ABSTRACT

Penile cancer is a rare malignancy and a debilitating condition in most industrialized nations that often requires aggressive surgical or multimodal treatment with significant anatomical, functional, and psychosocial impact on patients' quality of life. Total or partial penile amputation has been considered the standard of treatment according to locoregional clinical staging and risk stratification. However, these surgical options are associated with significant negative functional and psychological outcomes in terms of body image, self-esteem, and manhood resulting in loss of sexual function and inability of upright voiding. Recently, a critical paradigm shift has taken place in the clinical management of penile malignancy, that is, the implementation of alternative, less-invasive surgical strategies to deal with the primary malignancy. These sparing approaches of penile anatomy aim to retain penile and urinary functions and overall quality of life and thus interfering as little as possible with functional anatomy. This paradigm shift has been made possible by advances in surgical and technological developments which have resulted in organ-preserving strategies with gratifying psychosocial and functional outcomes simultaneously without compromising final cancer control. This spectrum of novel surgical strategies includes local excision, glansectomy, and partial penectomy followed by surgical reconstructive procedures consisting of primary closure of the resulting defect, closure with skin flaps or split-thickness skin grafts, penile lengthening and/or enhancing procedures, neophalloplasty, and, more recently, penile transplantation fostered by limitations of conventional reconstruction. This review discusses the complexities of surgical reconstruction following penile cancer treatment including the burgeoning field of penile transplantation.

Keywords: penile cancer, functional outcomes, penile reconstruction, organ sparing, organ preservation, glansectomy, penile reconstruction, phalloplasty, penile transplantation

Introduction

Penile cancer is an uncommon disease in high-resource, industrialized countries accounting for < 1% of male cancers [1]. However, its incidence is estimated at 2.3 – 8.3 per 100,000 men in South America, Africa, and Asia, which raises clinical management issues for the urologist [2, 3]. The rarity of the disease, its variable clinical presentation, delay in seeking medical attention likely due to lack of awareness, fear, embarrassment, shame, and sense of guilt, as well as potential misdiagnosis by the initial physician are negative factors that often lead to delay in diagnosis and, subsequently, less optimal treatment outcomes and dismal implications on prognosis. Hence, radical surgical management options have traditionally been the cornerstone of treatment associated with very good long-term oncological outcomes. However, the amputating consequence of this radical surgery leads to serious physical, sexual and psychological morbidity [4].

The diagnosis of penile cancer prompts patients to be worried about their sexual function and body image, especially sexually active men. These concerns commonly make them reluctant to undergo mutilating treatment that will affect their body image and self-confidence. This scenario led urologists to develop surgical therapeutic options that are capable of addressing both physical and psychological issues of these patients, ultimately resulting in a major shift in paradigm from "mutilation" to "preservation" [5-7]. Therefore, contemporary penile preservation in the surgical management of penile cancer has assumed a leading position, with the simultaneous objective of achieving good oncological control with the least impact on anatomy, function, and psychosexual health of the patient [8].

This review will focus primarily on the contemporary penile-preserving surgical options utilized in the management of the primary penile neoplasm, including surgical innovations related to organ preservation as well as reconstructive techniques. More recently, penile transplantation has become a new emerging frontier in restoring sexual function, body image, and self-confidence in patients considered cured of their penile cancer.

Evidence for Penile-Preserving Surgical Strategies for Penile Cancer

The surgical management of penile cancer depends on the biologic characteristics of the disease, specifically its clinicopathologic grade and stage. Although a few urologists may argue the role of traditional radical amputating surgery in the treatment of advanced stage T4 or high-grade stage T3, or more proximal stage T2 cancers, many are currently questioning the need to perform this highly aggressive surgery in less advanced, lower grade and stage cancers. Historically, it was widely accepted that at least a 2-cm tumor-free margin was considered a good oncological margin after penile cancer surgery to achieve an adequate and safe clearance. Fueled by patients' concerns regarding body image and sexual function, this concept of mutilating surgery has led to an important change in the clinical approach to penile cancer and the promotion of penile-preserving options in the surgical management of penile cancer.

Agrawal et al. analyzed pathologic specimens of 64 patients who underwent partial and total penectomy and tried to determine the microscopic spread of the primary lesion beyond the macroscopic cancer margin [9]. This study concluded that 81% of the specimens did not extend beyond the macroscopic tumor margin. Of those that did, only 5% spread more than 5 mm from the tumor margin. Consequently, the authors proposed a 10-mm surgical margin would be adequate and safe for lower grade disease (grade 1 and 2). In another study, Hoffmann et al. did not find any recurrence at 33-month follow-up of their 14 post-penile amputation patients and 50% of their patients had a surgical healthy margin of < 10 mm [10]. Another important study by Minhas et al., 90% of the patients with a < 20-mm margin (48% of them was < 10 mm), only 6% of patients had positive pathologic margins and 4% developed local tumor recurrence within 26 months of follow-up [11]. In 2018, Sri et al. evaluated 332 penile cancer patients who underwent penile preserving surgery. In 64% of them had < 5-mm negative surgical margin and 16% had margins < 1-mm surgical margin clearance [12]. They showed that in their series local recurrence after penile preservation surgery was 4% only. Patients with significant risk factors for local recurrence developed cavernosal involvement and lymphovascular spread. Their final conclusion was that a deep clear margin of > 1 mm carries a very low risk of local recurrence in penile-preserving surgery [12].

The evidence for penile preservation strategies and its potential benefit has also been explored in the salvage of local recurrence following radiotherapy which may occur in up to 40% of cases [13]. Shabbir et al. treated 17 patients for chronic ulceration after radiation treatment. Of the 14 who underwent glansectomy with neophallus formation, all had a successful graft take and 13 patients were cured

without tumor recurrence at 3 years of follow-up, showing that a potential role in this cohort seems to be highly beneficial.

Indications for Organ-Preserving Surgical Strategies

The surgical management of penile cancer is mainly determined by the pathologic grade and stage of the disease. This will influence the selection of the most appropriate penile preserving surgical option for a specific patient. Other relevant factors such as the location of the primary lesion (whether or not involving the external meatus), patient's age, comorbidities, and risk factors, as well as issues related to body image (impact on penile length), sexual function and psychological effects must also be considered.

Penile preservation therapeutic strategies include medical and surgical modalities. Medical strategies include Moh's micrographic surgery, topical applications, laser, radiotherapy, and cryotherapy. Surgical modalities basically consist of partial and total glansectomy, wide local excision, and partial amputation.

The management of distal, noninvasive disease as well as invasive penile cancer may involve more than surgery alone. Other options including topical chemotherapy, immunotherapy and radiation therapy may be necessary. Providing that patients are good candidates for penile preservation management, have been informed adequately on cancer recurrence and commit themselves to rigorous close surveillance, excellent functional outcomes and oncological control can be expected. Since the follow-up for penile-preserving surgery is more demanding and exhaustive than penile amputation, a compliant, well-informed subject is a critical prerequisite for penile preservation procedures. Pathologically, the ideal candidate will be a low stage, Tis/Ta or T1. Some patients with T2 disease and well to moderately differentiated tumor grade, penile preservation may be a reasonable option [14]. Penile preservation can also be offered to a few well-selected patients with urethral involvement that is confined to the glans and with negative intraoperative frozen section specimens [15]. Usually, tumors that are suitable to penile preservation are located on the distal segment of the penis such as prepuce, glans, and distal penile shaft. On the contrary, in cases in which complete tumor excision with pathologically negative margins as confirmed by intraoperative frozen section is not possible, they should not be offered penile preservation techniques. Similarly, if the remaining penile stump is inadequate (< 3-4 cm in length) for a forwarded directed urinary stream, these patients should not undergo penile preservation. It is critical to focus on the criteria to identify suitable patients for penile preservation management options, we will discuss the surgical techniques employed and functional outcomes following these procedures. Medical treatment such as topical applications, laser treatments, radiotherapy, and cryotherapy will not be the scope of this review (Table 1).

Table 1. Penile Preservation Surgical Options and Their Clinicopathologic Indications

Penile Cancer	Penile Preservation Strategies
Tis	Topical chemotherapy Laser ablation (CO_2; Nd:YAG) Moh's micrographic surgery Glans resurfacing Circumcision (prepuce only)
Ta, Tia (G1, G2) and T1a	Laser ablation Moh's micrographic surgery Radiotherapy (BT/EBRT) Glans resurfacing Circumcision (prepuce only) Wide local excision Glansectomy + reconstructive Surgery (STSG)
T1b (G3) and T2 (involving glans only)	Glansectomy + reconstructive surgery (STSG)
T2 up to T3	Distal corporectomy/partial penectomy

CO_2 = Carbon Dioxide; Nd:YAG = Neodumium-doped: Yttrium Aluminium Garnet; BT = brachytherapy; EBRT = External Beam Radiation Therapy; STSG =Split-Thickness Skin Graft

ORGAN-PRESERVING SURGICAL MANAGEMENT BY PENILE CANCER STAGE

For Tumor Stages Up to T1a

Moh's Micrographic Surgery (MMS). MMS is predominantly a classical technique characterized by excising all the abnormal lesion in a regular and spatial fashion in thin horizontal tissue "slices" with simultaneous histopathological frozen section examination until achieving negative surgical margins microscopically [16]. It aims to preserve normal penile tissue as much as possible with minimal complications. The typical indications are low grade lesions, such as carcinoma in situ, verrucous penile lesions, lesions of the glans or distal penis, and patients who wish penile preserving surgery [17].

Some authors reported 5-year survival >85% with MMS for patients with low-stage penile cancer. However, the local recurrence rate was relatively high, occurring in 8 of a total of 25 patients (32%) [18]. In this study, 8% had inguinal node recurrence and succumbed to the disease. However, Mohs FE et al. reported that 23 of 29 (79%) patients were cured at 5 years [19].

The advantages of this surgical technique are good and meticulous tumor mapping as well as penile lesion excision with negative margins can be achieved leading to penile preservation and better cosmetic and functional outcomes. However, MMS has not become very popular in treating penile cancer as it includes important limitations, such as a local recurrence rate of 32%, only 50% cure rate for legions >3 cm, and, therefore, applicable to a limited number of candidates as acknowledged by Mohs himself and others [18, 19]. Additionally, the procedure requires considerable supporting staff and is costly.

For Lesions Confined to the Prepuce (Tumor in situ, Ta, T1/grades 1 and 2)

Circumcision. Uncircumcised, mostly elderly, men presenting with phimosis with concurrent bleeding and/or a palpable lump under the foreskin is highly suspicious for penile cancer. Circumcision is the most common procedure in the surgical treatment of penile cancer, being ideal and sufficient in patients with penile tumors confined exclusively to the prepuce, especially if the tumor is small and in the distal portion of the prepuce. However, if the tumor is larger and more proximal, circumcision and distal penile shaft excision may be warranted. Intraoperative frozen section examination is critical. A curative wide local excision may be achieved by circumcision alone if adequate negative surgical margins can be confirmed by frozen section pathology [20]. In some cases, the preputial lesion extends toward the penile shaft skin and coronal sulcus, requiring a more extended aggressive excision and split-thickness skin grafting for resurfacing the penile stump [21, 22]. Bissada et al. concluded that option alone should suffice as primary curative treatment for small low stage and grade lesions (Tis, Ta, and T1; grades 1 and 2). However, Pietrzak P et al. found recurrence rates as high as 50%, in these more proximal tumors calling for careful and meticulous selection of candidates for the procedure [22]. Finally, circumcision is always recommended before radiotherapy as it allows better exposure, targeting, and better definition of the penile lesion [23].

For Tumor Stage - Tumor in situ (Tis) up to T1a

Glans Resurfacing. The first description of glans resurfacing is attributed to Depasquale et al. in 2000 for the treatment of balanitis xerotica obliterans [24]. It has become the standard surgical treatment for penile glans lesions from Tis up to T1a, not impacting penile length and function negatively (Figure 1). Other potential candidates are patients who failed topical chemotherapy or laser treatment and cases with extensive field involvement and even up to Ta tumors with <50% glans involvement [25]. In this procedure, both the glandular epithelium and subepithelium are removed. If <50% or >50% of the glandular surface is removed, these are termed partial glans resurfacing (PGR) and total glans resurfacing (TGR), respectively [26, 27]. This procedure gained its roots from the treatment of lichen sclerosis of the penile glans [26, 28].TGR involves marking followed by excision of all glans epithelium and subepithelium while sparing the peri-meatal and circum-coronal margins. This excision is made in quadrants from the urethral meatus to 1 cm beyond the coronal sulcus including deep biopsies of the spongiosum to confirm negative surgical margins. A split-thickness skin graft is harvested from the inner thigh to cover the defect using an air dermatome (Figure 2). Similar surgical steps are used for PGR with improved cosmesis and sensation. Graft take is usually excellent ranging from 96% to 100% [26, 28, 29]. No cancer-specific deaths were reported, and no morbidity was reported in 3 important studies totaling 71 patients with median follow-up of 21 – 30 months. It is associated with quick recovery, swift return of glans sensation, and good preservation of sexual function [26, 28, 30]. There were no local recurrences in these 3 studies. However, non-excisional alternatives such as laser treatment showed an unexpected 20% invasive disease rate in their final histopathology [26, 28]. Notwithstanding the obvious benefits of glans resurfacing, a high rate of margin positivity reaching 48%, and re-operation rate of 25% remain challenging [26]. Therefore, patients should be aware of the need for further surgery, eventually partial or total glansectomy.

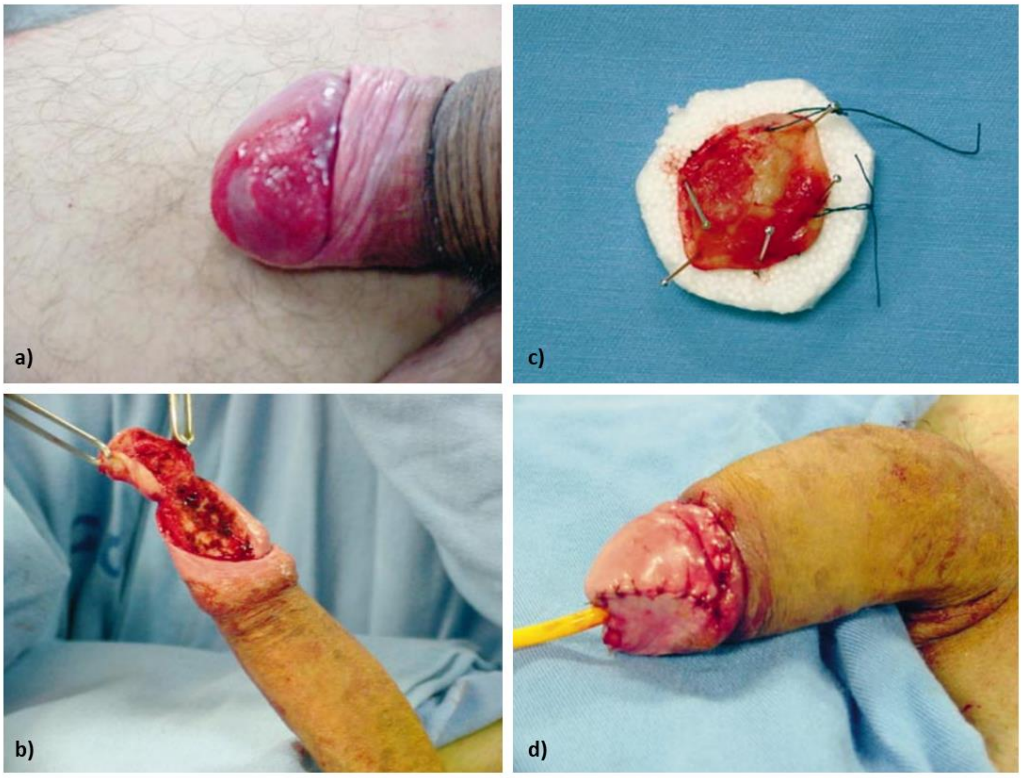

Figure 1– a) Preoperative view of glans-restricted tumor in uncircumcised patient; b) Lesion at completion of excision (dorsal view) ; c) Resection of tumor specimen; d) Final aspect after reconstruction using the foreskin pedicle flap (dorsal view). *(Reprinted with permission. Lima MVA et al. Acta Urológica Portuguesa 2007;24: 4:33-37)*

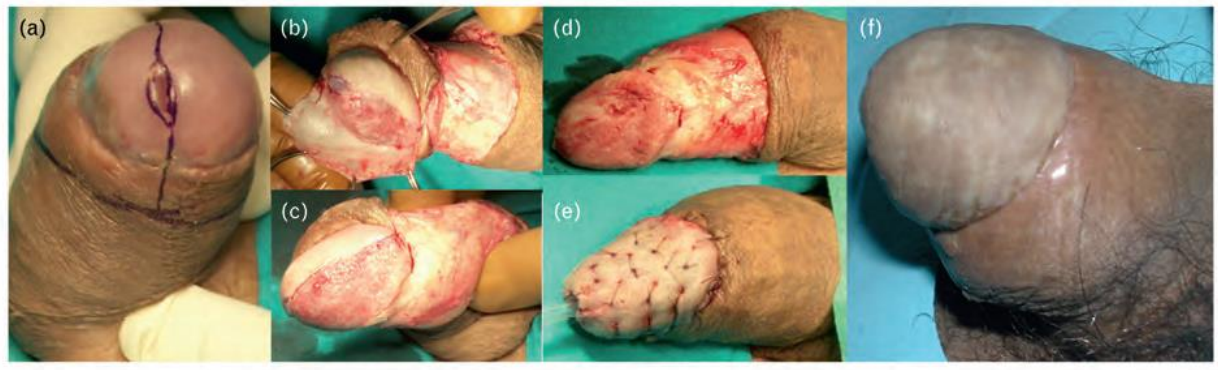

Figure 2– Glans resurfacing. (a) Preoperative appearance. (b–d) Glanular epithelium is fully removed up to the coronal sulcus. (e) Glans is resurfaced using a free skin graft. (f) Outcome after 6 months. *(Reprinted with permission. Djordjevic ML et al. Curr Opin Urol 2014, 24:427–433) [Ref. 33]*

For Tumor Stage Ta up to T2

Glansectomy. More than 50% of penile tumors originate on the glans penis [31]. Large tumors that involve the glans and eventually grow into the distal urethra should be managed by glansectomy. This surgical procedure was initially described by Austoni et al. in 1996, and it has been used for Ta up to T2 tumors that are confined to the glans [32] (Figure 3). Penile disassembly has also been described as a preserving surgical option for penile glans tumors involving the distal urethra [33] (Figure 4). Glansectomy can be done partially or totally for excision of distal tumors of the penis (glans and prepuce) [22, 26, 34]. Frozen sections of the cavernosal and urethral surgical fields must be obtained to confirm margin negativity. An end-shaft urethrostomy is then performed.

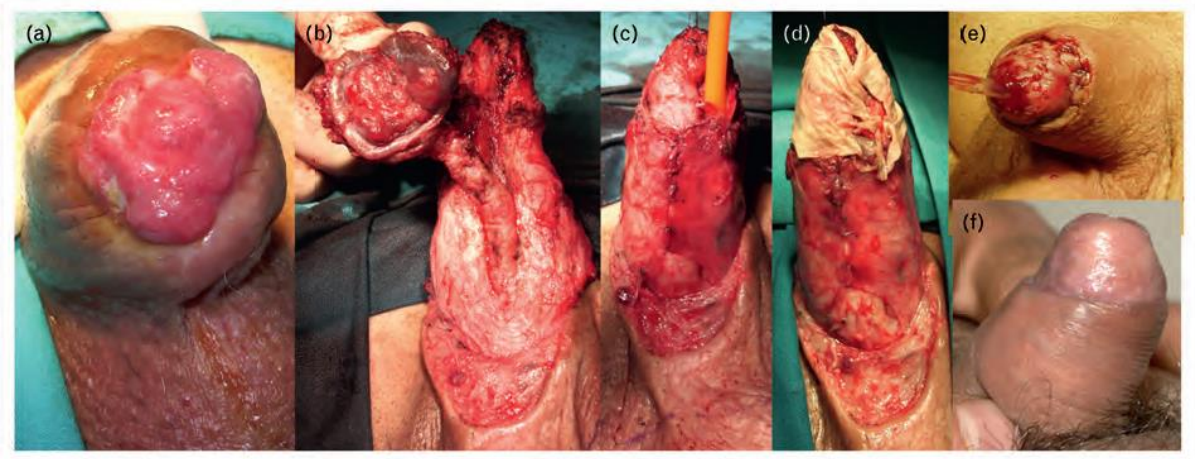

Figure 3– Glansectomy and neo-glans reconstruction. (a) Squamous cell carcinoma involving the glans and part of foreskin. (b) Glans with distal urethra is separated from the tips of the corpora cavernosa. (c) After removal of the glans, new urethral opening is created. (d) Split-thickness skin graft is used to cover the tips of the corpora cavernosa. (e) New glans is created by quilting the skin graft. (f) Outcome after 3 months. *(Reprinted with permission. Djordjevic ML et al. Curr Opin Urol 2014, 24:427–433) [Ref. 33]*

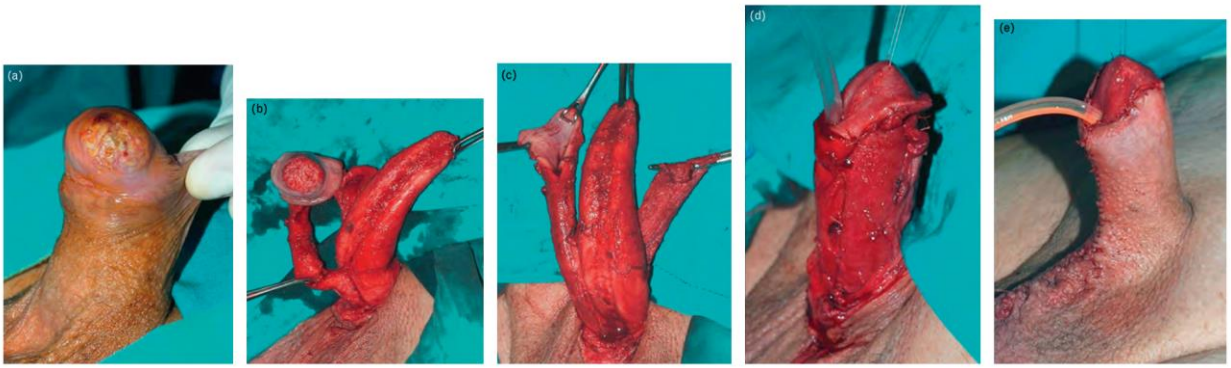

Figure 4– Penile disassembly for penile preserving surgery due to penile carcinoma. (a) Carcinoma involving the whole glans and distal urethra. (b) Penis was disassembled into anatomical parts: glans cap with urethra and neurovascular bundle, and corpora cavernosa. (c) After removal of the affected glans and urethra, distal urethra was mobilized and spatulated ventrally. (d) Newly created urethral flap was used for covering the tips of the corpora cavernosa, creating a new glans. (e) Outcome at the end of surgery. *(Reprinted with permission. Djordjevic ML et al. Curr Opin Urol 2014, 24:427–433) [Ref. 33]*

Partial glansectomy or wedge excision is recommended for patients with low-grade, small lesions up to T1a of the corona or central glans without surrounding involvement by Cis or corporeal involvement on MRI. Primary closure with minimal glans deformity may be used if the defect is of small size. In cases where larger tumors are intrinsically associated with larger defects, this procedure will require excision of the affected portion of the glans followed by a split-thickness skin graft (STSG), advancement of the penile shaft skin or a preputial cutaneous flap to achieve satisfactory function and cosmesis. The STSG must be harvested from a non-hair bearing donor site, typically the inner thigh. Full thickness skin grafts and mucosal grafts are not recommended due to their poor graft take, especially if exposed to dry environment (especially, oral mucosa), and resultant poorer cosmetic outcomes [31]. Subtotal glans excision without grafting has been described as a simple and cosmetic conservative option for penile cancer [35]. These authors reported that spraying of urine can be reduced with preservation of distal urethra, a phenomenon universally observed following total glansectomy. These patients should undergo a close postoperative surveillance protocol for early detection of any local relapse [32].

Total glansectomy is the best surgical approach for T2 or high-grade T1 tumors. These lesions usually invade the tunica albuginea and/or cavernosal tissue. An incision 1 cm below the coronal sulcus is

made until the Buck's fascia and a sharp surgical plane is developed between the corporal tips and glans. Frozen sections of the surgical bed should be taken to confirm margin negativity. The corporal body tips are sutured together, and the neo-glans is reconstructed using a STSG. Alternatively, if cosmesis and/or sexual function are not important concerns for patients, advancement of the penile skin over the corpora can be performed and a STSG will not be necessary. An important concern for the patient is penile length with potential impact on sexual and voiding functions. Surgical techniques to address this problem include division of the suspensory ligament of the penis, or a staged scrotal skin reconstruction, this latter option being particularly useful as a corrective procedure for previous surgical attempts leading to a trapped penile stump [36]. Mon pubis liposuction may also be helpful as an adjunctive procedure, and in some cases a penile prosthesis may be necessary [25]. Complications associated with total glansectomy and STSG reconstruction may include urethral narrowing, graft failure and graft contracture, which were reported as 8% in the literature [15, 37]. Because some T2 lesions can be quite large and apparently advocating for a more aggressive surgical approach, Emmanuel A et al. recommend evaluation with penile MRI and frozen section pathology to confirm the presence of tunica albuginea invasion and guide the initial dissection more proximally on the penile shaft [25].

Very satisfactory oncological outcomes have been achieved with glansectomy and reconstruction in several studies. Parnham et al. carried out a study on 177 patients after glansectomy and STSG in the UK. With a mean follow-up was 41 months, the local recurrence rate was 9.3%, mortality rate of 10.7% and reoperation rate due to meatal stenosis and graft loss was 9% [38]. Smith et al. reported a recurrence rate of only 4% at a 27-month follow-up on a similar study with 72 post-glansectomy patients [15]. Another study reported a local recurrence rate of 6% in a cohort of 87 patients with a mean follow-up of 42 months [39]. Regarding sexual function after glansectomy, Seidigh et al. reported a 59.1% reduction in genital sensation and a 9.1% loss of erogenous sensation. However, ejaculation was maintained in 68.2%, as well as a reduction in erectile function, orgasmic function, and global satisfaction as assessed by IIEF-5 questionnaire [40]. In another study by Morelli et al., although sexual preservation was good, all patients reported reduced glans sensitivity [41]. Some authors have reported on women complaining of dyspareunia following glansectomy by their male partners, likely resulting from loss of the cushion effect of the glans [42].

For Tumor Stage T2 up to T3

Wide Local Excision/Distal Corporectomy/Partial Penectomy. A more extensive and deep removal is recommended for penile cancers invading the corporal bodies or urethra. Partial resection is warranted coupled with successive frozen sections of the surgical bed until negative margins are demonstrated. Then the remaining penile stump is assessed for the chances of reconstructive and lengthening procedures to achieve an acceptable functional and cosmetic result. Up to 2 cm in length can be obtained by dividing the suspensory ligament just inferior to the pubic arch. However, penile lengthening procedures can be delayed until definitive clinical and histopathological staging is confirmed.

The standard technique of partial penectomy has been extensively described. Traditionally, a 1-2 cm safety margin proximal to the lesion is recommended for the circumferential incision, which is made to deglove the penis, mobilizing the shaft skin to expose Buck's fascia. The corpora and urethra are transected proximal to the lesion, taking special care to leave the urethra with about 1 cm longer than the corpora for an adequate ventral spatulation and reconstruction of the neo-urethral meatus. The penile shaft skin is advanced distally and sutured 2-3 cm from the penile tip. The neo-glans can be reconstructed with a STSG or, in patients for whom cosmesis and sexual functional is no longer important, then the STSG may not be needed, and the penile skin advancement will be used to create the neo-glans. The remaining penile stump should be sufficient for forward directed urinary stream, otherwise total penectomy should be recommended. Partial penectomy is associated with local recurrence rate up to 8%, preservation of sexual function in 20% and voiding in the standing position in the majority of patients [14, 43]. In the same study by Bissada et al., the meatal stenosis occurred in 6% [43].

In younger patients, or in those with no comorbidities and still interested in pursuing with their sexual function, penile length is a critical patient concern. Several techniques have been suggested to increase penile length and girth (Table 2).

Table 2. Surgical Techniques for Penile Lengthening and Enhancement

Division of the suspensory ligament
Corporal mobilization from the undersurface of the pubic arch
Horizontal incision of the penoscrotal skin followed by longitudinal suturing
Surgical correction of a penoscrotal web at the ventral aspect of the penis
V-Y plasty at the pubic area
Liposuction of the pubic area
Insertion of a penile prosthesis

Excellent oncological outcomes may be achieved with wide local excision/distal corporectomy/ partial penectomy with no local recurrences reported in one study involving 227 patients [44].

Sexual Function and Psychosocial Effects After Penile Cancer Management

The sexual and psychosocial effects of penile cancer management, especially partial penectomy, have not been well documented. Most of the studies in this area of limited research have included studies with small sample sizes. Most studies on sexual function are related to partial penectomy. However, sexual outcomes of penile preserving therapies, including glans resurfacing and glansectomy, have also been explored and, not surprisingly, have shown less severe detrimental effects on the sexual and psychosocial aspects of patients' quality of life.

Effects of glans resurfacing and glansectomy. Hadway P et al. studied the sexual function of 7 patients after glans resurfacing. All patients were sexually active 3-5 months after the operation, and all reported that the glans sensation was either the similar or improved post-surgery [28]. All patients had erections within 2-3 weeks of surgery and 6 were engaged in sexual intercourse 3 months post-surgery. Overall satisfaction was also high, and 5 of them even considered there had been an improvement in their sexual life [28]. Similar results have been reported with other conservative treatments such as CO2 laser therapy, confirming the low impact on sexual life of patients with penile cancer [45, 46].

Effects of partial penectomy. The international index of erectile function (IIEF-5) was used to report sexual function covering 5 distinct domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. Although not under the IIEF-5 umbrella, self- esteem and social relationship will be discussed briefly in this review. In a systematic review by Whyte E. et al, 4 studies were analyzed in detail [47]. Three of these studies reported an important decline in all independent IIEF domains after partial penectomy; in contrast, one study reported an increase in all sexual function domains according to IIEF-5 questionnaire (except for orgasmic function, which declined) [48-51]. In the study by Romero FR. et al, 50% of patients with no sexual activity reported feeling of shame due to a smaller penis size and absence of glans as the main cause for the lack of sexual activity and interest [48]. Therefore, maintaining as much penile length as possible, along with keeping current safe surgical margins of 3-5 mm can allow better preservation of penile length [52]. Overall, the bulk of evidence shows that there is a decline in sexual function after partial penectomy for penile malignancy. Nonetheless, a number of patients can still maintain pleasurable sexual function following surgery, mainly if longer penile stumps can be preserved, and in younger men.

Reconstructive Surgical Options: Penile Lenghtening, Augmentation, and Phalloplasty

Complex penile reconstruction following penile cancer amputating surgery constitutes a serious challenge to surgeons and patients alike. Despite nearly a century of great efforts and growing experience in penile reconstructive strategies, the creation of the ideal neophallus continues to puzzle the surgical reconstructive community. Nikolaj Bogoraz from Russia is credited with the first attempt at total penile reconstruction in 1936 [53]. He used a bipedicle abdominal flap with a rib cartilage to ensure rigidity for possible sexual intercourse. However, this procedure failed to meet the urethral reconstruction requirements for adequate voiding as well as protective and/or erogenous sensation. In 1948, expanding on this technique two British plastic surgeons introduced the modern "tube within a tube" pattern for the construction of the neourethra [54]. The drawback of this technique was the need for ≥3 stages and the highly inconsistent results.

With the introduction and swift expansion of microsurgery in the field of complex urogenital reconstruction, significant improvements have been achieved in terms of functional and cosmetic outcomes which are highly beneficial psychosocially in patients who have achieved proper oncological

control. Despite these advancements, there is no global consensus on the best reconstructive technique. Additionally, complications are common and potentially catastrophic.

Penile lengthening and enhancement techniques. Several surgical techniques have been described in the literature to restore penile length and enhance penile function for both traumatic loss of the penis or partial penectomy for penile malignancy (Table 2). The primary goal is to regain penile length and outward protrusion to enable standing urination and sexual intercourse.

The release of the suspensory ligament with detachment of the proximal corpora from the pubis, eventually combined with surgical fixation of the released corpora at the pubic symphysis or placement of a spacer at the release area is a good option to avoid adhesions and penile retraction. Other options, either used alone or in combination, have included surgical correction of a ventral penoscrotal web, creation of a neo-glans creation from the remaining penile shaft, additional penile release maneuvers infrapubically and ventrally, and partial thickness skin grafting of the Buck's fascia of the exposed penile shaft combined with lipectomy of the suprapubic area [55, 56].

Neophalloplasty. Total phalloplasty is one of the most challenging endeavors in genital reconstruction for both patient and surgeons. This operation is reserved for men who have suffered extensive or total penile loss due to penile cancer or trauma. Phallic reconstruction is meant to create a penis to allow resumption of sexual function. Neophalloplasty involves microsurgical free tissue flap reconstructive techniques with different sources of donor site graft material (Table 3).

Table 3. Phalloplasty Options	Pros	Cons
RFFF	"Gold standard" technique? Low total flap loss rate Good neophallus sensation High orgasm rate High patient satisfaction Sensation +++	High urethral complication rate
ALT	Used as pedicled or free flap Sensation ++	High urethral complication rate Functional/cosmetic results??
FOF	Avoid penile prosthesis Sexual intercourse Good satisfaction Sensation ++	Potential bone resorption Risk of bone element fracture Difficult control of rigidity Flap loss similar with others High urethral complication
LDMF	Reliable/versatile Relatively easy technique Large surface area Long and robust pedicle Well concealed donor site Good function and aesthetics Good neophallus size Easy penile prosthesis insertion	Poor erogenous sensation Deficient orgasmic sensation Risk of penile implant erosion Sensation +
ASF	Most straightforward option Quick recovery Good length and girth Minimal donor site morbidity Placement of Penile Prosthesis	Closure difficult if obese No urethra in 1st stage Sensation +

RFFF = Radial Forearm Free Flap; ALT = Anterolateral Thigh Flap; FOF = Fibular Osteocutaneous Flap; LDMF = Latissimus Dorsi Myocutaneous Flap.

In 1987, Gilbert and Winslow described the five requisites for an ideal phalloplasty [57]: 1) a reproducible procedure that can be performed in a single stage; 2) creation of a neourethra that allows standing urination; 3) a phallus with erogenous and tactile sensation; 4) sufficient bulk to allow the implantation of a penile prosthesis and, therefore, enabling penetrative vaginal intercourse; and 5) a satisfactory esthetic result.

Surely, these five goals must consider the donor site morbidity, as all techniques require tissue transfer maneuvers from other parts of the body to restore the missing urethra, penile shaft skin, and penile soft tissue bulk. Meeting these criteria with conventional surgical options continues to challenge surgeons' creativity for more than three decades.

Several conventional surgical techniques of neophalloplasty have been described which have the potential to achieve the five listed goals described by Gilbert and Winslow: 1) radial forearm free flap (RFFF); 2) anterolateral thigh flap (ALT); 3) fibular osteocutaneous flap (FOF); 4) latissimus dorsi myocutaneous flap (LDMF); and abdominal or suprapubic flap (ASF). All these flap techniques, and to our knowledge the most popular, allow for the transfer of a large amount of tissue in a single stage with acceptable donor site morbidity [58, 59]. Essentially, each one of these flaps has its pros and cons, and therefore the selection of the donor site should rest on the combination of the individual patient's preference and the surgeon's ability to generate a consistently optimal result.

A. Radial Forearm Free Flap (RFFF; Free Flap). This flap is one of the most commonly used for neophallus reconstruction and considered to be the modern "gold standard" technique by some. However, despite being the "gold standard" procedure, its outcomes fall short in several ways. In a meta-analysis by Yao et al. involving 925 patients, urethral fistulation rate was around 30%, although 41% of which were managed conservatively [57]. Urethral strictures occurred in only 8.2% of these phalloplasties. However, total flap loss rate was low at 1.5%, and partial/distal flap loss of 7.4% [58]. Monstrey et al. reported similar results with overall urologic complication rate of 41% and need to remove penile implants in 44% [60]. Overall, patients' satisfaction is good and 75%-100% report the ability to urinate while standing as well as satisfaction with cosmesis, and neophallus sensation range from 80% to 97%. After successful innervation, 80% of these patients reported to be able to achieve orgasm [61].

B. Anterolateral Thigh Flap (ALR; Local Pedicle Flap). The ALT flap is based on blood supply from perforators of the descending branch of the lateral circumflex femoral vessels. It can be fashioned as either a pedicled or free flap for neophallus creation. Published functional and cosmetic results are not abundant and dependent on significant heterogeneity in surgical technique and results. Urethral fistula formation at a rate of 22% and urethral stricture at a rate of 7% are the most common complications [62].

C. Fibular Osteocutaneous Flap (FOF; Free Flap). Fibular osteocutaneous flap is a common technique that involves a vascularized osseous component in order to provide long-term stiffness avoiding the need for a penile prosthesis. The main disadvantages of this flap are the potential bone resorption, risk of fracture of the bone element, and the difficulty to control the rigidity of the neophallus, as in the case of a penile implant [58]. FOF largely shares similar outcomes with other flaps already mentioned, specifically flap loss, either total or partial, in up to 2% and 15%, respectively. Urethral fistulation and urethral stricture are the two most common complications [58]. Yet, most patients report standing voiding, have sexual intercourse, and feel satisfied altogether [58, 63].

D. Latissimus Dorsi Myocutaneous Flap (LDMF; Free Flap). Perovic et al. have published extensively on the use of this flap in total phalloplasty with very good results in both pediatric and adult patients [64-66] (Figure 5). First described by Baudet et al., LDMF is reliable and versatile for free-tissue transfer. It is relatively easily elevated, with a large surface area, and nourished and innervated by the thoracodorsal artery and thoracodorsal nerve, respectively, which constitute a large, long, and robust pedicle [67]. The LDMF well concealed location, its potential for primary closure, relatively hairless donor site, and a great bulk of tissue are the basis for a functional and aesthetic reconstruction. It allows for a direct anastomosis with the femoral artery without venous interposition. Some major concerns associated with LDMF are its poor erogenous sensation, lack of orgasmic sensation of the flap which can impact satisfactory sexual activity. Another potentially serious disadvantage is the risk of penile prosthesis erosion due to the low protective sensitivity of the neophallus. Overall, LDMF can provide very good neophallus size with good aesthetics. Implantation of a penile prosthesis is easy and sexual intercourse is highly satisfactory.

Figure 5 – a) The delineation of the LDM flap; the flap plan includes the superior and anterior limits of the latissimus dorsi muscle; the thoracodorsal artery course is shown; the flap base is marked at the hilum and extending downward with 11-15 cm in width and 13-18 cm in length; these flap dimensions and glans location are drawn according to the standard penile size. b) Final appearance of the LDMF phallus. c) Lateral view of the post-harvest LDMF scar and phallus. *(Reprinted with permission.* Perovic SV, Djinovic R, Bumbasirevic M, Djordjevic M, Vukovic P. Total phalloplasty using a musculocutaneous latissimus dorsi flap. BJU Int. 2007 Oct;100(4):899-905; discussion 905 *[Ref. 64]*

E. Abdominal or Suprapubic Flap (ASF; Local Pedicle Flap). Abdominal or suprapubic phalloplasty is an option for gender-affirming genital surgery in transmasculine and nonbinary people [68]. Abdominal suprapubic phalloplasty is a local pedicled flap that uses skin and fat from the lower abdomen to create a new phallus. It is rated as the most straightforward phalloplasty option and offers the fastest recovery for patients. It can be performed either as a single stage pedicled phalloplasty for patients who desire a phallus but do not wish to stand to urinate or want an erectile implant or as a staged procedure with subsequent urethroplasty and penile implant placement. The key advantages of abdominal phalloplasty include a satisfactory phallus length and girth, the absence of a microsurgical anastomosis, homogeneous skin color of the phallus and the groin, and an inconspicuous donor site scar. Donor site morbidity and the risk of other complications are relatively minimal when compared to other phalloplasty options. However, the presence of excessive fat can make harvest site closure difficult. Limitations may include a lack of nerve coaptation to the dorsal clitoral nerve, thick subcutaneous tissue limiting tubularization, and potential for variability in the blood supply. A further limitation to this type of phalloplasty involves shaft reconstruction only. The urethra is not typically constructed in the first stage, but its construction is possible to allow standing urination later.

Penile Transplantation: A New Frontier

Penile transplantation is an emerging option for patients with severe penile loss, either due to trauma or cancer, which are not ideal to traditional reconstructive techniques. The aims of penile transplantation are the following: 1) adequate standing voiding; 2) allowing natural erections; 3) recovery of erogenous sensation; and 4) normal appearance of male genitalia. According to the Baltimore Criteria for an ethical approach to penile transplantation, recipients should be adults who were victims of significant phallus loss due to trauma (following ≥ 6 months of recovery) or due to cancer (with ≥ 5-year remission), or were born with ambiguous genitalia, and for whom other reconstructive options are not feasible or unacceptable to the recipient. These individuals must have passed clinical, physical, and psychological assessment and aspire to achieve normal functional and quality of life (esthetic, urinary and sexual). The deceased donors (age ranging from 16 to 65) should be matched for age (maximum 5 years) and skin tone whenever possible, with a healthy and functioning potential graft. These surgical procedures must occur at approved transplant centers with a multidisciplinary team involving reconstructive urologists, plastic surgeons, psychiatrists, infectious disease physicians, and bioethicists. Recipients should be meticulously informed of all risks surrounding transplantation, especially lifelong immunosuppression issues [69].

In penile cancer patients, it should only be considered after long-term remission and cure has been achieved. A 5-year remission period has been considered standard after oncologic penectomy. The largest study to date that evaluated recurrence after penile cancer treatment showed that all local and distant recurrences occur in the first 5 years [70].

Animal models for penile transplantation were developed in the early 2000s involving rat models [71, 72]. The first technically successful penile allotransplantation performed in a human subject occurred in Guangzhou, China in 2006. The recipient was a 44-year-old man who had sustained severe traumatic loss in an accident. However, the graft was explanted two weeks later because of psychological rejection by both the patient and his wife [73]. In 2015, the Tygerberg Hospital surgical team in South Africa led by Dr. van der Merwe carried out the first successful penile transplant on a 21-year-old male after traumatic penile loss sustained during ritual circumcision [74, 75]. Two years later, the transplant recipient was urinating well, and had erections, orgasm, and ejaculation [75]. In 2016, Cetrulo et al. in the US performed a partial penile transplant to a 64-year-old man post-amputation for penile cancer. The graft was obtained from a deceased donor [76]. This patient also reported recovery of penile sensation, successful voiding, and partial erectile function 6 months post-operatively.

Finally, in the US in 2018, an *en bloc* transplantation including the entire penis, scrotum, and part of the abdominal wall was performed from a deceased donor to an injured veteran who sustained blast injury to the abdominal wall and perineum. One year post-operatively, the patient had recovered normal micturition, erogenous sensation and full erection, reporting that his transplanted phallus feels "normal" [77].

Most debates on the use of penile transplantation have focused on traumatic causes. Recently, the indications have been expanded to victims of penile cancer amputation. Historically, penile transplantation has been reserved as the last resort after repeated unsuccessful attempts at phalloplasty [78]. However, this idea has been recently challenged in the international reconstructive community, based on the important disadvantages of going through multiple failed reconstructive attempts before transplantation [79]. Several benefits to engaging in transplantation before running out of options for phalloplasty, specifically the superior functional and cosmetic results of transplantation, outweigh its inherent risks for some patients. Additionally, there may be no adequate remaining salvage techniques for penile reconstruction if the transplant fails.

Critical anatomical considerations must be followed. The penis should be harvested with the urethra as proximal as possible just as for penectomy. The arterial system of the penile allograft should be flushed with ice-cold transplant solution at around 3° Celsius until the fluid draining from the penis is clear. Preparation of the penis for transplantation should begin immediately after the penis is cooled sufficiently to 3°- 4° Celsius. All the necessary microscopic vascular surgical tool setup should be ready for the surgeons in an isolated environment with the least human personnel traffic as possible to avoid colonization of the allograft [70]. Interestingly, most local recurrences occurred after penile preserving strategies in this study. A potential argument in favor of a negligible risk of locoregional recurrence is that all remaining native penile skin is excised before transplantation [70].

As in all transplantation scenarios, immunosuppression is vital and should be kept as minimal as possible. Bone marrow infusion of donor bone marrow was conducted in the second US patient to maximize immunological tolerance. The recipient, a young war veteran, has been maintained on a single dose of tacrolimus [80].

Ethical issues are extremely important when dealing with recipients of, or potential candidates to, a penile transplant. The significant risks and collateral effects should be communicated to patients in the lengthy work-up and preparatory period before surgery. Therefore, the value of the informed consent cannot be overestimated, and it remains one of the most pivotal ethical pillars.

Penile transplant recipients will require lifelong surveillance by a multidisciplinary team to assess physiological functions, psychosocial balance, as well as respective complications originating from these domains and from chronic immunosuppression. It is critical for both patient and surgeon to guarantee the most desired benefits of the complex reconstruction, such as sensation, urinary and sexual function.

Conclusion

Several organ preserving surgical strategies have been developed for patients who require surgical management for their penile oncological condition. These treatment options should maximize functional and cosmetic outcomes, simultaneously minimizing related physiological and psychosocial impact,

whilst assuring excellent cancer control in the same way as traditional, more radical techniques. Patient selection for these organ-preserving therapeutic options is paramount but patients are equally responsible to follow closely the postoperative surveillance programs so any oncological recurrence can be detected early, and salvage treatment can be instituted.

Several phalloplasty techniques have been introduced for the restoration of fundamental bodily functions such as standing urination and sexual activity, as well as improvement of quality of life. These phalloplasty techniques have gained popularity as common flaps utilized in penile reconstruction; however, they are often associated with complications, and may need various surgical stages and revisions before a satisfying result is obtained. Penile transplantation represents a revolutionary step in the treatment of penile loss due to trauma or cancer. It is safe if all preoperative issues, specifically careful patient selection and well-shared informed consent with patient and his family are addressed. While still in its infancy, significant technical and pharmacological strides have been made in the field of penile transplantation to provide the recipient the best physiological functions possible, including standing urination, erogenous sensation, the ability to achieve an erection and an unparalleled aesthetic outcome.

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