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Penile cancer and phallus preservation strategies: a review of current literature

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Penile cancer is a rare malignancy in most developed nations but its management can have significant anatomical, functional and psychological effects in patients. Whilst total penectomy used to be widely practiced, it is associated with significant psychological consequences pertaining to body image and masculinity, with loss of sexual function and the ability to void upright. Recent advances in surgical techniques and technologies has allowed for many organ-sparing techniques with acceptable psychosexual and oncological outcomes. Factors to be considered in phallus preservation treatment include: local invasion, tumour stage and the ability to achieve complete oncological control. Topical chemotherapeutic agents, laser ablation, radiotherapy, Mohs micrographic surgery, glansectomy and partial penectomy have been frequently used to interfere as little as possible with functional anatomy without compromising local cancer control. The difficulty with these phallus-preserving techniques is the potential risk of disease recurrence both locally and distally. Providing that patients are suitable for penile-sparing therapy, have been informed adequately on risk of tumour recurrence and are willing to commit to rigorous close surveillance, good functional outcome as well as oncological control can be achieved.

Keywords

penile cancer, phallus preservation strategies, clinical outcomes, penile surgery, radiotherapy, glansectomy

Introduction

Penile cancer is a rare malignancy in most developed nations but its management can have significant anatomical, functional and psychological effects in patients. The highest incidence of penile cancer is reported in developing countries, such as Brazil (2.9–6.8 per 100 000) and parts of Africa (up to 20%) [1]. There is a significant variation in world geographical incidence, and this may be explained by the different aetiologies of penile cancer, e.g. smoking, hygienic practices, religious and cultural beliefs. In Australia, squamous cell carcinoma of the penis is a rare malignancy with an estimated incidence of 0.6–0.9 per 100 000 [2], which is on par with other Western countries. Cancer Council Australia estimated that of the 114 137 newly diagnosed cancer cases, 82 cases of penile cancer were found and 17 cases of mortality were registered in 2010 [2].

The first step in the histological diagnosis of penile cancer is the confirmation of the diagnosis and assessment of the depth of invasion by microscopic examination of the biopsy specimen, followed by cancer staging. The treatment option for penile cancer is complete cancer eradication. Whilst total penectomy used to be widely practiced, it is associated with significant psychological consequences pertaining to body image and masculinity, with loss of sexual function, as well as the ability to void upright. Recent advances in surgical techniques and technologies has allowed for organ-sparing techniques with acceptable psychosexual and oncological outcomes [3–5]. For the purpose of this review, the focus will be solely on phallus-preserving strategies in penile cancer. The role of imaging studies, use of sentinel node biopsy and lymph node management are outside the scope of this discussion. Factors to be considered in phallus preservation include tumour stage, local invasion and the ability to achieve complete oncological control. It is for the aforementioned reasons, that phallus preservation strategies should be considered.

Surgery of Primary Tumour: Phallus-Preservation Strategies

Primary treatment options for penile cancer can be categorised based on location of tumour and extent of tumour invasion. While the traditional approach to treating penile cancer has been total penectomy, different therapeutic options

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Table 1 Advantages and disadvantages of various penile preservation strategies.

Treatment	Indication	Advantages	Disadvantages
Topical chemotherapy	Carcinoma *in situ*	Moderate efficacy	Prolonged therapy; less effective in immunocompromised
Radiotherapy (BT/EBRT)	Lesions <4 cm on glans/coronal sulcus	Cosmesis	Meatal stenosis and urethral strictures; penile pain, ulceration, necrosis and infection
Laser	Tis/T1 disease	Good functional and cosmetic results; few complications	High recurrence rates, up to 48%
Mohs surgery	Tis to T2	Preservation of uninvolved penile tissue	High recurrence rate ≈30% but majority salvageable with further Mohs
Circumcision	Preputial disease – premalignant/ low grade, low stage	Curative therapy for low grade low stage	High recurrence rates, up to 50%
Glansectomy	T1/T2 disease	0.5 cm margins safe with no local recurrence after complete glansectomy	Loss of graft, stenosis; decreased penile sensitivity
WLE ± split-skin graft	T1 disease	Avoid partial penectomy	High recurrence rates, up to 27% especially in T2 tumour; associated penile deformities
Partial penectomy	Disease extension (e.g. T3 tumour); failure other conservative measures	Standard of care for distal penile tumour	Meatal stenosis; changes in urinary and sexual function

have been developed to preserve a functional phallus, although some are not without major limitations (Table 1). Phallus-preserving strategies for primary penile cancer in the foreskin, glans and shaft of penis can be divided into medical and surgical interventions.

Medical Therapy

Topical chemotherapeutic agent

Topical chemotherapy, e.g. 5-flurouracil (5-FU), and more recently immune response modifiers, e.g. imiquimod 5% and interferon α-2a cream, is indicated for superficial and/or premalignant penile lesions, e.g. carcinoma *in situ* (Bowen's disease and Erythroplasia of Queyrat) and bowenoid papulosis [6, 7]. Its role in the treatment of superficial penile cancer has been reported with variable success. The cream is applied directly onto the lesion for 4–6 weeks.

The advantages of topical chemotherapy include simple application, low rates of toxicity and adverse events. The disadvantages include risk of prolonged therapy (average duration of treatment of 4–6 weeks with estimated healing time of 4–8 weeks) and poor therapeutic efficacy in immune-compromised patients.

Laser ablation

Laser therapy, either carbon dioxide (CO_2) [8] or neodymium-yttrium-aluminium-garnet (Nd:YAG) [9,10], has been successfully used as a first-line therapy for premalignant lesions and early stages of penile cancer since the 1980s. The indication for the use of laser therapy is superficial penile cancer, either Tis or T1 disease. The CO_2 laser has a tissue penetration of 0.1 mm, while Nd:YAG laser penetrates to a depth of 4.2 mm. Contraindications to laser therapy include tumour with >6 mm depth invasion and T2 tumour. A recent paper reported that T2 penile cancers treated with laser therapy are associated with an increased rate of lymph node metastasis at follow-up [9].

The advantages of laser therapy include good functional and cosmetic outcomes, avoidance of surgery, and that oncological outcome and survival are not affected by local recurrence [11,12]. The disadvantages of laser therapy are high recurrence rates, reported to be between 3.1% and 48% [9,10]. The Nd:YAG laser can cause significant tissue coagulation and prevent accurate histological diagnosis, resulting in under-staging of the disease [13]. While the CO_2 laser does not cause significant tissue coagulation, it is limited by its lower tissue penetration compared with the Nd:YAG laser.

Cryotherapy

Cryotherapy involves the use of liquid nitrogen to achieve temperatures of –20 to –50 °C to cause tissue damage by cellular membrane disruption and subsequent cell death. Cryotherapy is more commonly used in the treatment of genital warts and premalignant lesions than for penile cancer. A study comparing cryotherapy and topical 5-FU in the treatment of Bowen's disease showed that the risk of recurrence after cryotherapy (13.4%) was greater than after 5-FU treatment (9%) [14].

Radiotherapy

The two forms of radiation therapy used in the treatment of penile cancer are external-beam radiotherapy (EBRT) [15] or brachytherapy (BT) [16, 17]. The typical EBRT schedule is 4000 cGy in 20 fractions over 4 weeks to the entire shaft of the penis with the primary lesion and margins receiving an additional 0.02 Gy booster dose. There are two common BT techniques described in the literature. First, is a radioactive mould placed over the penis and is worn by the patient for 12 h/day for 7 days. This delivers ≈0.6 Gy to the tumour and 0.5 Gy dose to the urethra. The other technique involves the implantation of a radioactive iridium (Ir 192) seed into the penis and this is removed when the predetermined dose has been delivered. Circumcision should be performed before radiotherapy with glans tumour to reduce radiation-induced

complications. BT offers good success rates particularly for low-stage disease and in general is more successful than EBRT. 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 [17]. Indications for EBRT include superficial or exophytic lesions of <4 cm, and tumour located on the glans or coronal sulcus. Lesions of <4 cm on the glans penis with no tumour extension onto the shaft may be suitable for BT [17,18]. However, a recent study has shown that BT can be effective in T2 and selected T3 penile cancer [16]. Radiotherapy may be offered to patients medically unfit for surgery or as palliative treatment. Contraindications for EBRT or BT include any penile tumour of >4 cm with concurrent inguinal lymphadenopathy.

The proposed advantages for radiotherapy include good long-term cosmesis and excellent rate of penile preservation [19]. The disadvantages of radiotherapy are skin pigmentation, telangiectasia, long treatment duration and healing time. After EBRT healing can take 6–8 weeks and in those receiving BT can take up to 2–3 months. Urethral adhesions with deviated stream and urethral strictures are not uncommon sequelae from radiation. Meatal stenosis is another known late complication, with reported incidence at 10–45% at 3 years after radiation therapy. Radiation-induced penile ulceration or necrosis can occur between 7 and 18 months after treatment in up to 23% of cases and may require debridement or amputation of penile tissue [16,18].

Surgery

Foreskin – circumcision

Most patients with penile lesions are uncircumcised. The indications for circumcision are preputial disease, low-grade and low-stage penile cancer. It is also indicated for acquired phimosis secondary to preputial tumours, especially before radiotherapy. Alone, circumcision is curative for low-grade, low-stage preputial disease [20,21]. The disadvantage of circumcision is the reported recurrence rate of 50% at 2 years, indicating a need for regular close surveillance [20,21].

Glans – Mohs surgery

Mohs micrographic surgery involves excision of tissue layers, a single layer at a time, and potentially could be used over several sessions with concurrent microscopic evaluation to ensure that a tumour-free plane is obtained. The indications for performing penile Mohs surgery are carcinoma *in situ* or verrucous carcinoma, lesions of the distal penis or glans penis, otherwise amenable to partial penectomy, and a desire for penile preserving surgery [22]. The 5-year survival rate has been reported at >85% of cases [23]. The success rate is shown to be stage dependent [22,23]. Contraindications to Mohs surgery include advanced tumour stage, those amenable to partial penectomy and in instances where the involvement of the urethra or the size of the defect outweighs potential cosmetic or functional results.

The advantages of the Mohs technique include proper tumour mapping and excision of the tumour with no positive margins, and preservation of uninvolved penile tissue with improved cosmetic or functional outcome. The disadvantage of the Mohs technique is poorer local control as evidenced by the high rates (≈30%) of local recurrence after one procedure [23]. However, most recurrences were suitable for further Mohs surgery. Complications, e.g. meatal stenosis or glans disfigurement, have been reported.

Glans – glansectomy

Up to 80% of penile squamous cell carcinomas occur distally, either on the glans or prepuce, and so may be amenable to glansectomy [20,24]. Glansectomy may either be partial or complete and is commonly performed with split-thickness skin grafting. Intraoperative frozen section should be undertaken to ensure negative surgical margin before the reconstructive procedure. If tumour extends to the underlying tunica albugenia or corpora cavernosum, distal corporectomy should be performed. Depending on the size of the defect, partial glansectomy is described by three techniques: (i) it may be primarily closed, (ii) closed with a lateral preputial or scrotal skin flap, or (iii) with skin grafting [25–28].

Indications for glansectomy are lesions limited to the glans or prepuce [29]. Partial glansectomy is indicated for T1 lesions. A T2 lesion may be treated by complete glansectomy. New studies have shown that a margin of 0.5 cm is oncologically safe [30]. The disadvantages of this procedure include potential cancer recurrence in the remaining glans tissue after partial glansectomy [27,28]. In cases where grafting has been used there is also the risk of loss or contraction of graft, or graft overgrowth over the external urethral meatus. Decreased penile sensitivity has also been described and in men with total glansectomy, a loss of penile length is a common complaint [26–28,31].

Shaft – wide local excision (WLE)

WLE may be performed in conjunction with primary closure or split-skin grafting. Although a 2-cm surgical margin has been traditionally proposed, more recent data suggest that for low-risk tumours a 10 mm clearance is adequate for grade 1 and 2 lesions, and 15 mm for grade 2 tumours [32]. WLE can be performed for pre-cancerous lesions, discrete lesions, extensive preputial disease where circumcision alone is not curative and T1, low-grade tumours of the shaft. Lont et al. [33] found that of the patients with T2 tumours treated with penis preservation, regional recurrence in not uncommon (27%) but can be treated accurately in most cases. Contraindications to WLE include: tumour in close proximity to the urethra, urethral involvement or lesions extending more than half of the glans penis. The disadvantages may include potential tumour recurrence [34] and significant deformity or deviation of the penis during erections.

Shaft – partial penectomy

Partial penectomy remains the standard care for men with distal penile cancer [35,36]. More recently glanuloplasty with urethral flap after partial penectomy has been described with satisfactory functional and cosmetic results and an acceptable complication rate [37]. The indications of partial penectomy are disease extension into the urethra or corporal bodies, and/or local recurrence of disease after previous more conservative attempts at treatment. Proximal extension of penile cancer beyond such that partial penectomy would not achieve a functional residual penile remnant is a contraindication. In these cases, total penectomy is advised. A recent paper compared laser therapy, WLE and radiotherapy to partial or total penectomy, showed that local disease recurrence rates were lower with the latter treatment (5.3% vs 27.7%) but there was no significant difference in overall disease survival [38]. However, the presence of local recurrence after partial penectomy carries a poor prognosis [33].

Partial penectomy offers excellent local control with low recurrence rates (<10%) and allows for preservation of urinary function and possible sexual function [39, 40]. The most common complication is neo-urethral meatal stenosis.

Conclusion

While penile cancer is uncommon, it has significant psychological and physical effects on the patient. Many patients delay in seeking medical attention due to embarrassment, fear, and/or ignorance. The ideal outcome involves the preservation of normal sexual and urinary function while eradicating the disease. However, often due to extent of disease this is not always possible. It is understandable why patients often are reluctant to undergo radical treatment due to the devastating effect it has both physically and psychologically. It is for this reason that there is a range of organ-preserving strategies that matches the clinical spectrum of patients presenting with penile cancer (Table 1).

Table 2 Selected contemporary data on various penile preservation strategies.

Reference	Year	Stage	Patient number	Technique	Local recurrence rate, %	Follow-up, months
Windahl et al. [11]	2003	Tis–T2	67	Laser (Nd:YAG, CO_2)	19	Median 42 (12–186)
Lont et al. [33]	2005	T1–T2	104	Excision, laser (Nd:YAG, CO_2)	37.5	Median 106 (16–543)
Meijer et al. [13]	2007	Tis–T2	44	Excision, laser (Nd:YAG)	48	Mean (SD) 53.2 (43.3)
Bandieramonte et al. [8]	2008	Tis–T1	224	Excision, laser (CO_2), chemotherapy	17.5	Median 66 (35–132)
Leijte et al. [38]	2008	Tis–T2	289	Laser (Nd:YAG, CO_2)	27.7	Median
			105	Local excision		60.6 (3–358)
			21	Radiation therapy		
Schlenker et al. [9]	2010	Tis–T2	54	Nd:YAG	42	3–66
Alnajjar et al. [7]	2012	Tis	44	Chemotherapy	13.6 – partial response 29.5 – no response	Mean 34
Ozsahin et al. [19]	2006	T1–T3	21	External RT	61	Median
			7	External RT, BT		62 (6–454)
			1	BT		
Mistry et al. [15]	2007	Tis–T3	17	External RT	37	-
Crook et al. [16]	2009	Tis–T3	67	BT	13	Median 48 (4–194)
Shindel et al. [23]	2007	Tis–T3	33	Mohs	32	Median 37 (0.5–214)
Pietrzak et al. [26]	2004	Ta–T3	39	Partial glansectomy up to partial penectomy	3	Mean 16
McDougal [24]	2005	T1–T2	5	Partial glansectomy	13	Mean
			2	Excision of shaft skin		32 (12–60)
Palminteri et al. [31]	2007	Tis–T2	1	Glans resurfacing	0	Mean
			11	Glansectomy up to partial penectomy		32 (12–60)
Philippou et al. [30]	2012	T1–T3	13	Circumcision	8.9 – Local	Mean (SD)
			29	WLE	10.6 – Regional	42.8 (25.6)
			137	Glansectomy	5.0 – Distant	
Feldman and McDougall [34]	2011	Tis–T1	2	Moh's	21.4	Mean (SD)
			11	Circumcision		65.64 (46.56)
			25	WLE		
			14	Partial Glansectomy		
			4	Topical Chemotherapy		
Li et al. [29]	2012	Tis–T2	8	Circumcision	9.4	Median 26.5
			18	WLE		
			6	WLE + circumcision		
O'Kane et al. [28]	2011	Tis–T3	25	Glansectomy + SSG	4	Mean 28

Topical chemotherapeutic agents, laser ablation, radiotherapy, Mohs micrographic surgery, glansectomy, WLE and partial penectomy have been frequently used in order to interfere as little as possible with penile functional anatomy without compromising on the oncological outcome. However, each of these penile-preserving techniques and treatments has its own limitations and the decision on the choice of treatment is dependent on the tumour location, size and stage, as well as patient factors, e.g. health status and treatment preference. One of the biggest limitations with these treatments is the potential risk of disease recurrence both locally and distally (Table 2) [7–9,11,13,15,16,19,23,24,26,28,29,30,31,33,34,38]. Topical chemotherapeutic agents use should be restricted to premalignant or *in situ* cancer only. Radiation can be used as an alternative to surgery in selected cases, but unfortunately, few patients with penile cancer are candidates for radiation therapy. Penile-preserving surgery may offer a better functional outcome and may be judiciously used in selected cases with rigorous use of intraoperative frozen section, and close surveillance providing the patient is aware of the increased risk of local recurrence and the potential implications.

Conflict of Interest

None declared.

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Abbreviations: BT, brachytherapy; EBRT, external-beam radiotherapy; 5-FU, 5-flurouracil; Nd:YAG, neodymium-yttrium-aluminium-garnet (laser); WLE, wide local excision.