# Penile cancer: current challenges

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SIOW WY, CHENG C. Penile cancer: current challenges. The Canadian Journal of Urology. 2005;12(Supp 1):18-23.

Penile cancer remains a formidable challenge in many developing countries because of its high incidence and the advanced disease stage at diagnosis.

For early penile cancer, surgery alone offers a high cure rate. Penile sparing therapies are proposed as alternative treatment options for select patients with the added advantages of preservation of body image and improved quality of life.

#### Introduction

Penile cancer is rare in developed countries. It is chiefly a disease of the developing world and it represents a significant cancer in certain countries e.g. parts of India, China and Africa where the incidence may account for 17% of all male cancers.<sup>1,2</sup>

In Singapore, the incidence of penile cancer between the years 1968 and 1992 ranged from 0.7 to 1.4 per 100,000 population, representing 0.3 percent of all cancers in Singapore. There is a 1-year delay in diagnosis in 15% to 50% of the patients. This results in an advanced disease stage at diagnosis that translates to a poorer prognosis.<sup>3</sup>

Address correspondence to Dr. Christopher Cheng, Department of Urology, Singapore General Hospital, Outram Road, Singapore, 169608 The optimal management of lymph node disease remains controversial. The role of the sentinel lymph node biopsy, lymphatic mapping, prophylactic lymphadenectomy and the template for lymph node dissection are discussed.

For advanced, metastatic penile cancer, more effective and less toxic chemotherapy is needed. This may be coupled with palliative surgery or radiotherapy for the primary tumor and inguinal disease.

**Key Words:** penile cancer, lymphadenectomy, penectomy, chemotherapy, radiotherapy

#### Etiology

Smoking is one of the strong risk factors for the development of penile cancer with a dose-response relationship.<sup>4-6</sup> The other risk factors include phimosis and the presence of chronic inflammatory conditions.<sup>7,8</sup>

In contrast, neonatal circumcision is an established negative risk factor. This is associated with a three-fold decrease in the risk of penile cancer. Nevertheless, despite the apparent benefits, there is insufficient data to recommend routine neonatal circumcision.<sup>9,10</sup>

The etiologic relationship between balanitis xerotica obliterans (BXO) and squamous cell carcinoma (SCC) of the penis remains uncertain. Nevertheless, as chronic inflammation predisposes towards the development of penile cancer, some clinicians advocate active topical treatment of BXO, careful clinical follow up and surgical treatment of phimosis.<sup>11,12</sup>

The human papilloma virus (HPV) has been linked to both cervical cancer in the female and penile cancer in the male. HPV types 6 and 11 are considered low risk, whereas types 16, 18, 31 and 33 are high risk for malignant change. There is no positive relationship between penile cancer and the presence of cervical cancer in the patient's wife/ partner.<sup>13</sup>

In penile intraepithelial neoplasia, 70%-100% of lesions are HPV DNA positive, mostly of type 16, but in invasive penile cancer, HPV DNA is positive only in 40%-50%. Thus most studies suggest that HPV has an etiological role in penile cancer, although the attributable proportion may be only 40%-50%.<sup>7,14</sup> SCC of the penis exists in two morphological forms i.e. typical squamous form (non-HPV related) and warty/ basaloid form (HPV related).<sup>15</sup>

Premalignant lesions of penile cancer include erythroplasia of Queyrat, Bowen's disease, bowenoid papules and giant condylomas.

Tarnovsky first described the classical lesion in "Erythroplasia of Queyrat" in 1891. Thereafter, Queyrat coined the name in 1911. Well-defined, bright red, glistening, plaques on the glans penis and prepuce characterize the lesion. This condition usually occurs in the 5<sup>th</sup> and 6<sup>th</sup> decades of life. It is solitary in 50% of patients. Ten percent progress to invasive disease and 2% develop distant metastases.<sup>16</sup>

Bowen's disease was first described in 1912. It involves the penile shaft and is similar in appearance to Erythroplasia of Queyrat but for the absence of the red color. Five to ten percent of the lesions progress to invasive carcinoma and there is also a possible association with visceral cancers (respiratory, gastrointestinal and urogenital).<sup>17</sup>

Bowenoid papules refer to plaques on the penile shaft or perineum of young men. They have an indolent clinical course and respond to local treatment modalities. There is no progression to invasive cancer or association with visceral cancer. Spontaneous regression may also occur.<sup>18-20</sup>

Giant condyloma and condylomata acuminatum are both associated with HPV infection.<sup>21-24</sup>

In developing societies where penile cancer is common, poor penile hygiene, phimosis, smoking and human papilloma virus (HPV) 16 and 18 infection are the chief contributory factors towards the development of penile cancer. In addition, effective management of the cancer is often hampered by a delay in diagnosis and treatment attributable to ignorance, lack of access to health care and lack of funds.

Thus, simple public health measures e.g.

improving general hygiene standards, public education on smoking cessation and prevention of sexually transmitted diseases (STD) will play an effective role in curbing the disease in societies where it remains rampant.

In addition, there is a need for multi-centre studies and the pooling of results in order to increase our knowledge of penile cancer. The establishment of uniform staging systems and pathology reports will form the basis for this exchange of knowledge.

### Staging

There is a disparity between clinical and pathological staging of the primary tumor in about 25% of cases.<sup>25,26</sup> Ultrasonography (US) and magnetic resonance imaging (MRI) can provide adjunct information for the study of the male urethra and penis.<sup>27,28</sup> Since ultrasonography is superior to physical examination in the assessment of the primary lesion, routine use of ultrasonography should enable preservation of more of the penis.<sup>29</sup>

The regional nodal status in penile cancer has significant prognostic implications. In the absence of nodal disease, the 5-year survival is 77%. This decreases to 25% in the presence of inguinal nodal disease and 10% in the presence of pelvic nodal disease.<sup>30</sup> Unfortunately, the accurate assessment of lymph node status remains a challenge. Clinical examination is unreliable for this purpose. Computer tomography (CT) and MRI may be used to monitor regional lymph nodes especially after removal of the primary tumor. They remain optional investigations depending on the pathological characteristics of the tumor, the surgeon's experience and the availability of the tests. Lymphangiography is not recommended because of its pitfalls and limitations.<sup>31-33</sup>

The sentinel lymph node refers to the first filter in the lymphatic pathway and is the most likely regional node to harbor metastatic carcinoma.<sup>34</sup> Lymphatic mapping and sentinel lymph node biopsy for penile cancer was first reported by in 1977 by Cabanas.<sup>35,36</sup> Although penile cancer exhibits predictable lymph node involvement that follows a stepwise progression along the nodal echelon, use of the sentinel lymph node and even the extended sentinel lymph node biopsies remain unreliable.<sup>37-39</sup> The role of dynamic sentinel node biopsy using technetium 99 and gamma detection probe is still experimental.<sup>40,41</sup>

Pathological features of the primary tumor help in the prediction of regional lymph node involvement. Tumors staged T2 and above have a 61%-75% risk of lymph node disease. In contrast, T1 tumors are associated with a 5%-11% risk of nodal involvement.<sup>26,42</sup> Poorly differentiated tumors have a 75%-100% risk of nodal disease compared to 12%-50% for well and moderately differentiated tumors. Other pathological predictors for positive lymph node disease include presence of lymphatic and venous embolization and tumor thickness greater than 5 mm.<sup>43-47</sup>

#### Management of local disease

Options for the management of local disease include total penectomy, partial penectomy, circumcision, wedge resection, laser excision, cryotherapy, Moh's micrographic surgery (MMS) and radiotherapy.

Radical surgery provides the best oncologic clearance and penectomy, whether partial or total, is the standard surgical therapy for the local control of penile cancer. Local recurrence ranges from 0-5%.<sup>26,48,49</sup> Although the standard resection margin is 15 mm-25 mm, some studies have suggested that margins 10 mm or less may suffice.<sup>50</sup>

Undeniably, penile surgery has an immense psychological impact on many patients. In contrast, conservative i.e. penile sparing therapies allow for the preservation of body image and result in an improved quality of life. Premalignant lesions are best suited for penile sparing therapies.<sup>51,52</sup> Small (< 2cm), distal and low stage tumors may also be considered but penile conservation should not be attempted in T3 tumors.<sup>51,53</sup> Conservative treatment may also be appropriate for the elderly and infirm, in whom longevity is compromised and major surgery poses significant risk of peri-operative morbidity and mortality. Nevertheless, in cases where penile sparing therapies are desired and possible, a higher rate of local recurrence is expected, and, functional and aesthetic outcomes may not be excellent in all cases.<sup>54</sup>

Small lesions of the prepuce have been treated with circumcision alone, however, recurrence rates as high as 50% have been reported. Local wedge resection has also been associated with high recurrence rates of up to 50%.<sup>55</sup> The laser has been effectively utilized for the treatment of superficial tumors. Stages Tis and Ta tumors may be treated with CO2 or KTP lasers, while superficially invasive T1 tumors are best treated with more penetrating Nd:YAG or KTP lasers.<sup>56-59</sup> Attempts to treat T2 disease with laser have resulted in a uniform failure to control the disease.<sup>60</sup> The limitations of laser treatment lie in the treatment of the extremely obese patient, the immuno-compromised patient and patients on anti-coagulant therapy.

Cryosurgery is effective for T1-2, N0M0 penile cancers. It preserves penile function, offers excellent

cosmetic results and can be performed in the outpatient setting.<sup>61,62</sup> Topical 5-fluorouracil cream may be offered to the patient with carcinoma-in-situ.<sup>63-66</sup>

Moh's micrographic surgery was originally conceptualized for the excision of dermatological lesions with the twin aims of excising the cancer under total microscopic control while preserving the maximal amount of normal tissue.<sup>67</sup> It has been applied to penile cancer and may be a viable option for the treatment of small, localized tumors provided the surgeons and supporting staff are well versed in the technique.<sup>68</sup>

Local radical radiotherapy is an alternative treatment to surgery in selected stage T1 and T2 clinical node negative disease. Brachytherapy, external beam therapy or combination therapy may be suitable.<sup>69-71</sup> Adjuvant local radiotherapy may be needed in selected patients after partial or complete penectomy.<sup>72,73</sup> Local palliative radiotherapy may also be used for inoperable tumors and for patients who are unfit for palliative surgery.<sup>74</sup>

In view of the higher rate of local recurrence after penile sparing therapies, close follow up of such patients is needed. While most recurrences occur within 2 years of the primary treatment, recurrences after 10 years or more have been reported. With timely and appropriate salvage treatment, disease-specific survival is comparable to those who have undergone initial radical surgery.

### Management of lymph node disease

The optimal management of lymph node disease in penile cancer is one of the issues of greatest contention today. Although it is known that patients with negative and minimal nodal disease have a superior disease-specific survival compared to patients with overt nodal disease, there exists a great reluctance to offer routine ilioinguinal lymphadenectomy to all patients with penile cancer. The reason for this lies in the potential morbidity associated with the procedure. Up to 58% of patients may experience one or more complications e.g. seroma, flap necrosis, flap infection, pulmonary embolism and permanent lymphedema of the scrotum and lower limbs.44,45,75-77 The practical management of lymph node disease in penile cancer should thus be risk stratified based on histopathologic variables derived from the primary tumor.

Low risk disease refers to stage T1 grades 1-2, Ta and Tis penile cancer. Stage T1 penile cancer is associated with a 4%-14% incidence of nodal involvement and the chief predictor of nodal recurrence is tumor grade. With stage T1 grade 1 and 2 disease, nodal metastasis usually occur in less than 10% of cases, but with stage T1 grade 3 disease, nodal involvement may be as high as 81%. Lymphovascular invasion also portends a higher likelihood for lymph node recurrence. Since the likelihood of nodal disease for Tis and Ta tumors is even lower than that for T1 cancer, observation is a viable option for patients with clinically negative groin examination.<sup>78</sup>

For patients with low risk disease and palpable inguinal lymph nodes, inflammatory changes may account for up to 50% of nodal enlargement. Thus, re-evaluation is performed after 2 to 4 weeks of antibiotics treatment in the hope that inflammatory changes will resolve. Any palpable nodes should be examined by fine-needle aspiration and if the results are negative, an excisional biopsy should be performed. If the biopsy results are positive, then ipsilateral ilioinguinal lymphadenectomy with contralateral superficial or modified complete dissection should be performed.<sup>78</sup>

Patients with stages T2 and above penile cancer are at high risk for inguinal nodal metastases. The average risk is 59%. The management of the patient with node-negative, high-risk penile cancer should include local tumor control with bilateral superficial or modified inguinal lymphadenectomy with frozen section. Complete ilioinguinal lymphadenectomy is then performed if the frozen section results are positive.<sup>49,78-80</sup>

For patients with high-risk penile cancer and unilateral palpable inguinal nodes, local tumor control with ipsilateral ilioinguinal lymphadenectomy and contralateral superficial or complete modified dissection with frozen section analysis is recommended. Should the frozen section results be positive completion ilioinguinal nodal dissection will be performed on the contralateral side.<sup>78</sup>

Bilateral lymphadenectomy is performed for all patients undergoing lymph node dissection because crossover of penile lymphatics may occur in 50%-80% of cases. However, a full ilioinguinal dissection is not needed if microscopic examination of the superficial lymph nodes is negative. This is because; penile cancer shows a stepwise progression in nodal involvement along the nodal echelon with no bypassing.

Daseler proposed the original template for radical inguinal lymphadenectomy. The boundaries are superiorly- anterior superior iliac spine (ASIS) to external inguinal ring, laterally- line from ASIS extended caudally for 20 cm, medially- line from pubic tubercle extended caudally for 15 cm and inferiorlyline joining medial and lateral boundaries.

In view of the significant morbidity associated with

the radical inguinal lymphadenectomy, Catalona proposed a modified template for inguinal dissection. The boundaries are superiorly-line between spermatic cord and external inguinal ring, laterally-lateral edge of femoral artery, medially- adductus longus and inferiorly- fascia lata just distal to fossa ovalis.<sup>81</sup>

### Management of advanced disease

Patients with locally advanced and/ or metastatic penile cancer may be treated with chemotherapeutic agents used singly or in combination. Combination Cisplatin, Methotrexate and Bleomycin appears promising with a response rate of 32.5%, but the percentage of severe adverse effects is also high.<sup>82</sup> Chemotherapy may be administered systemically or regionally via a femoral intra-arterial catheter.<sup>83</sup> Palliative surgery or radiotherapy for the primary tumor and inguinal disease may also be needed.

#### Conclusion

Penile cancer remains a formidable challenge in many developing countries because of its high incidence and the advanced disease stage at diagnosis. In these areas, public health measures to improve the general hygiene and public education on the importance of early diagnosis will certainly result in a better outcome for patients.

In early penile cancer, penile sparing therapies have been explored to reduce the emotional impact of the disease. However, these options must be coupled with a strict surveillance program in order for early detection and effective treatment of local recurrences.

The optimal detection and management of nodal disease in penile cancer remains controversial. At present, the best predictors of nodal involvement are the histological characteristics of the primary tumor. With improved nutrition, advances in surgical techniques and better flap coverage, the morbidity of inguinal dissection will be reduced. This will allow more patients to safely undergo inguinal lymphadenectomy.

In locally advanced and metastatic penile cancer, there is a need for more effective and less toxic chemotherapeutic regimens. Finally, the role of radiotherapy for both the primary tumor and the regional nodes is not fully established.

To resolve the key issues and tackle the current challenges of penile cancer, prospective, multiinstitutional studies are needed to collectively increase our knowledge of the disease.

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