THE SURGICAL MANAGEMENT OF PENILE CANCER
AT THE FREE STATE ACADEMIC COMPLEX: A REVIEW

by

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DECLARATION

I, *Khotso Mohlomi*, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or at any other university.

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LIST OF ACRONYMS AND ABBREVIATIONS

AIDS	Acquired Immuno-Deficiency Syndrome
DSNB	Dynamic Sentinel Node Biopsy
EAU	European Association of Urology
ESMO	European Society for Medical Oncology
18FDG-PET/CT	18 Fluorodeoxyglucose (18F-FDG) Positron Emission Tomography/Computed Tomography
FNAC	Fine Needle Aspiration Cytology
FZ	Frozen Section
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
ILND	Inguinal Lymph Node Dissection
LVI	Lympho-Vascular Invasion
MILND	Modified Inguinal Lymphadenectomy
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
SCC	Squamous Cell carcinoma

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ABSTRACT

Introduction and aim

Currently there exist limited data about the management of penile cancer in South Africa and there are no centres of excellence for managing this malignancy. Therefore these patients are managed by different treatment strategies at different health facilities throughout the country.

The aim of this study is

i.   To describe the profile of men with penile cancer at our centre and compare it to the profile of men as described in the published literature
ii. To evaluate the incidence of histologically node-positive patients and the early complication rate of patients undergoing simultaneous inguinal lymph node dissection (ILND) during surgery for penile carcinoma and
iii. To describe the incidence of the different histological subtypes found at the Free State Academic Complex

Methods

Forty-one patients that presented with histologically confirmed penile cancer who were treated with surgery at the Free State Academic Complex between 2005 and 2015 were included. The data variables (that were analysed) included: Patients demographics, pre-operative penile biopsy results, type of surgery performed, results of final histology of primary penile cancer and dissected lymph nodes, and early lymph node dissection complications. Primary penile surgery and lymph node management were managed according to our evolving centre protocol.

Results

A total of 41 patients with histologically confirmed penile cancer were surgically treated. The mean age was 50 years (range 30-86 years). Human Immunodeficiency Virus (HIV) status was known in 20 patients and revealed positive results in 16 (80%) patients.

From a cohort of 41 patients, 25 patients underwent lymph node dissection for clinically palpable nodes or grade pT1 or higher disease. Of these 25 patients, eight patients (32%)

had lymph node metastasis, and 17 patients (68%) showed no evidence of nodal metastasis. Of the eight patients with positive nodes, five patients had unilateral groin positive nodes and three patients had bilateral groin involvement.

Out of 41 patients, 25 patients underwent primary penile surgery (glansectomy, partial (or) total penectomy with perineal urethrostomy) and inguinal lymph node dissection simultaneously. Complications associated with simultaneous penile surgery and lymph node dissection were seromas in two patients (8%), one superficial wound infection (4%) and 17 patients (68%) did not have post-operative complications. Five patients (20%) were lost to follow-up postoperatively.

All 41 patients (100%) had squamous cell carcinoma (SCC), and the predominant histological subtype was classic SCC in 36 patients (87%). This was followed by warty cancer subtype in three patients (7.3%), verrucous subtype in three patients (7.3%) and one patient (2.4%) had poorly differentiated cancer with spindle cell component.

Conclusion

Early age of presentation and high prevalence of HIV was observed in the present study which is in line with other published literature studies. Simultaneous primary penile surgery and inguinal lymphadenectomy can be done safely in a population with a high incidence of infection and HIV-associated lymphadenopathy. In our setting, where non-compliance and lost to follow-up rates are high, simultaneous primary penile and node dissection is advisable, but the importance of serial follow-up for recurrences and distal metastases cannot be ignored. The high incidence of node negative ILND in the current study was also observed. Penile cancer histological subtypes correlates with published literature despite high prevalence of HIV infection.

THE SURGICAL MANAGEMENT OF PENILE CANCER AT THE FREE STATE ACADEMIC COMPLEX: A REVIEW

CHAPTER 1

LITERATURE REVIEW

1.1 BACKGROUND

Penile cancer is an uncommon malignancy in the Western countries with an incidence of less than 1 per 100 000 men in Europe and the United States.[1] However, it is more commonly found in Africa, Asia and South America and accounts for 10% of all cancers in men in certain areas.[2,3] Some of the known risk factors include uncircumcised status, a history of condylomata accuminata, smoking, and possibly human papillomavirus (HPV) exposure.[4-6] The vast majority of malignancies of the penis are squamous cell cancers (SCC), but other histologic types are observed in 5% of cases. These histologic subtypes include melanomas, basal cell carcinomas and sarcomas.[7]

The peak incidence of penile cancers is in the sixth and seventh decades of life in Western countries.[8,9] There are a few randomized trials exploring treatment options for penile cancer and due to the small numbers of patients, management is typically based on retrospective reviews from large referral centres.[10]

In South Africa, the treatment of penile cancer is not centralized and patients are treated at different health facilities throughout the country. To date, there is limited data on surgical management of penile cancer in South Africa. Palpable inguinal lymph nodes are associated with proven nodal metastases in 43% of cases.[11] Historically a course of antibiotics was recommended for suspicious nodes to discern inflammatory nodes from metastases.[12] However, several authors have indicated that this surgical delay can impact on survival.[13,14] A course of antibiotics is no more advocated as a tool to select patients that should undergo inguinal lymphadenectomy.[15]

Ultrasound guided Fine Needle Aspiration Cytology (FNAC) can help to detect metastatic nodal involvement and is recommended by the 2009 EAU guidelines. According to literature there is 93% sensitivity and approximately 91% specificity after FNAC in patients with palpable nodes in predicting metastatic disease.[14]

The traditional surgical approach for penile malignancies has been partial or total penectomy, either with or without ilio-inguinal lymphadenectomy.[15,16] This surgical approach often results in marked cosmetic deformity of the penis, with impaired sexual function and poor body image.

In penile cancer, regional spread occurs from the inguinal nodes to the pelvic lymph nodes.[17] While inguinal lymph node involvement is one of the strongest predictors of survival in penile cancer the timing of inguinal lymph node dissection should be taken into consideration.[18] Inguinal lymph node dissection must be weighed against its associated morbidity. The need to balance the benefits of nodal dissection with its known morbidity has led to the development of models to decrease complication rate such as use of antibiotics, anticoagulation, modified inguinal lymph node dissection, use of suction drains, early mobilization, use of dynamic sentinel node biopsy (DSNB) and minimally invasive laparoscopic techniques.[19]

1.2 DIAGNOSIS OF PENILE CANCER

The glans penis is the most common site of origin followed by the prepuce, coronal sulcus and shaft.[23,24] Most patients present with localized disease such as a penile mass, ulcer or inflammatory lesion.[25]

1.2.1 Evaluation of primary penile tumour

Initial assessment of penile tumour should be made by physical examination. The physical examination of suspected penile cancer must record: diameter of the lesion, location on the penis, number of lesions, morphology of lesion (papillary, nodular, ulcerous or flat), relationship of the lesion to other structures such as submucosa, tunica albuginea, urethra, corpus spongiosum and corpus cavernosum; colour and boundaries of lesion and penile length. Physical examination alone can assess infiltration of the tumour into the corpora cavernosa. Where there is doubt as to the presence of corpora cavernosa invasion and to determine whether limited surgery is possible, magnetic resonance imaging (MRI) combined with an intracavernosal injection of prostaglandin E1 that causes an artificial erection may be helpful or ultrasound can give information about infiltration of the corpora.[26,27]

Accurate histological diagnosis and staging of penile tumour is of the utmost importance, this is supported by EAU, NCCN and ESMO guidelines.[28] The standard

approach of diagnosing a suspicious lesion is by punch, incisional or excisional biopsy. When performing a biopsy, the size of the biopsy is important, because this information helps in planning the treatment of the primary lesion and stratifying the risk for nodal metastases (i.e. in patients presenting with no palpable adenopathy).[29]

1.2.2 Evaluation of the inguinal region

Careful palpation of both groins for the detection of enlarged inguinal lymph nodes must be part of the initial physical examination of patients with penile cancer. Clinical examination of inguinal lymph nodes can often be inaccurate in detecting occult nodal metastasis, with false-negative rate of up to 25%, particularly in patients with adverse pathological features in the primary penile tumour.[30]

1.2.2.1 *Non-palpable inguinal nodes*

If nodes are non-palpable (cN0) during physical examination, the likelihood of the presence of micro-metastatic disease is about 25%. However, current imaging techniques are not reliable in detecting micro-metastases.[27] A FDG-positron emission tomography (PET) scan may be useful in detecting lymph node (LN) metastasis, however more data is still   needed. FDG-PET/CT imaging does not detect lymph node metastases <10 mm.[27] Ultrasonography can be used to identify inguinal LNMs, characterized by the distortion of the normal architecture. However, it is not sufficiently reliable.[27] A CT is valuable in identifying high-risk patients based on the presence of central node necrosis and irregular borders.[29]

Imaging studies are therefore not helpful in staging clinically normal inguinal regions. An exception can be patients with obesity in whom palpation is unreliable or not possible.[27] Dynamic sentinel node biopsy (DSNB) is a newer technique to assess clinically uninvolved nodes. DSNB is of less morbid approach with sentinel node identification rate of 97%, the false negative rate of 7% and the favourable complication rate of 4.7%, but it is still limited in several centres.[31,32] If DSNB is not available, ultrasound-guided FNAC biopsy of visualised nodes can be used.[6]

1.2.2.2 *Palpable inguinal nodes*

Palpable lymph nodes are highly suspicious for the presence of lymph node metastases. Physical examination should note the number of palpable nodes on each side and whether these are fixed or mobile. At the time of diagnosis, almost half of palpable inguinal nodes

are enlarged due to inflammatory changes, however, those that become palpable during follow-up are malignant in nearly 100% of cases.[11] The FNAC of all palpable nodes should be performed to rule out metastases supported by NCCN and ESMO guidelines. In case of a negative biopsy and clinically suspicious nodes, a repeat biopsy or node excision is advised. Additional inguinal imaging does not alter management and is usually not required, exceptions are obese patients, patients with prior inguinal surgery and those with suspected distant metastases.

MRI and CT scan can be performed to detect enlarged inguinal and pelvic lymph nodes. CT scan is used primarily according to ESMO guidelines despite its low reported sensitivity of 36%.[18] FDG-PET/CT is reported to have a high sensitivity of 88-100% with a specificity of 98-100% for confirming metastatic nodes in patients with palpable inguinal lymph nodes according to the EUA guidelines.[32] On the contrary, the ESMO reported that the use of FDG-PET/CT remains uncertain.

1.2.3 *Staging of penile cancer*

Penile cancer is staged according to the American Joint Committee on Cancer (AJCC) Tumour, Node, Metastases (TNM) guidelines **(Table 1)**. This staging system was initially introduced in 1968 and subsequently revised in 1978, 1987, 2002 and recently in 2010. In 2010 update, AJCC has made a distinction between clinical and pathological staging while eliminating the difference between superficial and deep inguinal metastatic nodes. Amongst the changes, T1 subdivided into T1a and T1b determined by the presence or absence of LVI or poorly differentiated cancers.[34]

TABLE 1.1: CLINICAL AND PATHOLOGICAL CLASSIFICATION OF PENILE CANCER (TNM, 2010)
(Table continue on next page)

Clinical classification	
T – Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
Ta	Non-invasive carcinoma
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)
T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)
T2	Tumour invades corpus spongiosum and/or corpora cavernosa
T3	Tumour invades urethra
T4	Tumour invades other adjacent structures

N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph node
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple unilateral or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Pathological classification	
The pT categories correspond to the clinical T categories. The pN categories are based upon biopsy or surgical excision.	
pN - Regional Lymph Nodes	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Intranodal metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of any regional lymph node metastasis
pM - Distant Metastasis	
pM0	No distant metastasis
pM1	Distant metastasis
G - Histopathological Grading	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated/undifferentiated

1.3 MANAGEMENT OF PRIMARY PENILE TUMOUR

1.3.1 Surgical treatment of the primary penile tumour

The surgical resection of the primary penile tumour involves complete removal of the cancerous lesion with penile preservation good as possible to preserve functional and cosmetic outcomes and avoid psychological distress. This is considered important in patients who develop penile cancer at a younger age (approximately 20% <40 years of age at presentation). According to literature, selecting the most appropriate technique is dependent on the following: stage and location of primary tumour, the effect of penile surgery on penile length, patients' age and comorbid conditions.[33]

1.3.1.1 *Stage Tis and Ta*

Tis and Ta are in situ and non-invasive lesions, respectively, and treated with penile preserving options including 5-fluorouracil or 5% imiquimod cream, local excision (total or

partial glans resurfacing) with or without circumcision, 44 carbon dioxide or neodymidium:yttriumaluminum- garnet (Nd:YAG) laser therapy, Mohs micrographic surgery, photodynamic therapy and glansectomy.[33,35] Penile-preservation strategies have been used more commonly in the recent years, as it has been recognised that this type of surgery for the primary cancer is associated with better functional outcomes and psychological well-being.[36] Negative surgical margin of 5 mm is considered oncologically safe and imperative when using penile-conserving treatments.[37,38] Success rates have been quoted that glansectomy and circumcision does have the lowest recurrence rate among the treatment modalities for small penile lesions (2%).[38] Fortunately, many studies does show that local recurrence after organ preserving surgery does not appear to have a negative impact on survival.[39,40]

1.3.1.2 *Stage T1*

<u>T1a</u>

All patients must be circumcised before considering conservative non-surgical treatment modalities. For all surgical treatment options, the intra-operative assessment of surgical margins by frozen section is recommended by EUA guidelines as tumour-positive margins lead to local recurrence. For tumours confined to the prepuce, radical circumcision alone may be curative, if negative surgical margins are confirmed by definitive histology. Category T1a lesions limited to the foreskin are superficial and can be managed by the same conservative approaches used in Tis and Ta disease.[27]

<u>T1b</u>

Category T1b lesions are now a distinct group from their T1a counterparts in the most recent AJCC staging system. For grade 3 (G3) and 4(G4) T1 penile tumours or those that demonstrate LVI (T1b) with increased risk of recurrence, more extensive surgical intervention with partial penectomy may be required for definitive local oncological control.[41]

<u>Stage T2</u>

Partial amputation with a tumour-free margin with reconstruction is considered the standard treatment.[37] A surgical margin of 5 mm is considered safe but patients should remain under close follow-up.[37,38] The recurrence rate of patients with resection margins of 5 mm or less

could still be <5%, and this has led to newer penile-preserving techniques being developed.[35]

<u>Stage T3 and T4</u>

Total penectomy with perineal urethrostomy is standard surgical treatment for T3 tumours as strongly recommended by EAU.[18,37] Total phallic reconstruction can be considered in appropriate patients.[42] In more advanced disease (T4) neoadjuvant chemotherapy may be advisable, followed by surgery in responders as in the treatment of patients with fixed enlarged inguinal nodes. Otherwise, adjuvant chemotherapy or palliative radiotherapy may be an option.[27]

1.4 SURGICAL MANAGEMENT OF REGIONAL LYMPH NODES

Lymphatic drainage from the primary penile tumour typically follows a systematic pattern. The superficial and deep inguinal lymph nodes are thereby the first regional nodal group reached by lymphatic metastatic spread.[33] Spread to the inguinal lymph nodes can either be unilateral or bilateral from any primary penile cancer. Pelvic LNs are the second regional nodal packet affected by lymphatic metastatic spread, and it typically occurs in the setting of ipsilateral ILN disease.[33] Pelvic nodal disease does not seem to occur without ipsilateral inguinal lymph node metastasis and cross-over metastatic spread from one inguinal side to the other pelvic side has never been reported in penile cancer.[34] Further metastatic lymph node spread from the pelvic nodes to para-aortic and para-caval nodes is outside the regional lymph node drainage system of the penis and is therefore classified as systemic metastatic disease.[27]

Prodigious management can be achieved in metastatic disease confined to the regional lymph nodes. Lymphadenectomy is the treatment of choice for patients with inguinal lymph node metastases but multimodal treatment combining surgery and poly-chemotherapy is often consired.[27] Management of the regional lymph nodes should, however, be stage-dependent. In clinically node-negative patients (cN0), there is a definite risk of micro-metastatic lymph node involvement in about 25% of cases which is related to local tumour stage and grade. In clinically positive lymph nodes (cN1/cN2), metastatic disease is highly likely (50%) and no time should be wasted on antibiotic treatment before surgical treatment. With enlarged fixed inguinal lymph nodes (cN3), multimodal treatment by chemotherapy and surgery is indicated. Capsular penetration and extra-nodal extension in lymph node

metastasis even if present in only one node carries a high risk of progression and is classified as pN3 which also requires multimodal treatment. [27]

1.4.1 Inguinal node management

1.4.1.1 *Non-Palpable inguinal node*

Sonar guided FNAC should be performed in all patients with non-palpable nodes, if it is positive, therapeutic setting rather than diagnostic lymphadenectomy can be implemented. Treatment options for clinically negative node include surveillance, Nomogram/risk-adapted lymphadenectomy, DSNB, modified ILND with frozen sections and elective bilateral radical lymphadenectomy.[26,27,34]

The management of inguinal lymph nodes in patients with normal groins on physical examination is dependent on the stage, grade and the presence or absence of LVI in the primary penile tumour.[33] The statistical probability of inguinal micrometastases can be estimated using risk group stratification or a risk calculation normogram, provided histopathological assessment of the complete primary lesions is available, not just a biopsy specimen. Tumours with low risk of inguinal metastatic spread (4%) include those that are G1 or G2 as well as pTis, pTa, and pT1 disease without LVI (pT1a).[32]

According to literature, data gained from an analysis of a variety of histopathologic variables within the primary penile tumour allow the classification of patients into the following risk groups for lymph node metastasis:

Low risk group – Tis, verrucous carcinoma (Ta), stage T1 grade 1
Intermediate risk group – Stage T1 Grade 2
High risk group – Stage T1 Grade 3 onwards[96]

Surveillence of inguinal regions is recommended if the probability of positive lymph nodes on the nomogram less than 0.1 (10%), alternatively if the primary lesion is G1, pTis, pTa (verrucous carcinoma) or pT1 and cN0 with LVI.[97] This is however, dependent on the patient is willing to comply with regular follow-up and provided obesity, prior inguinal surgery or radiotherapy do not prevent clinical assessment of the groins.[97]

Prophylactic ILND is regarded as a preferable option in socio-economic conditions which prevents regular follow-ups, despite the level of morbidity. In the intermediate risk group

(nomogram probability 0.1 to 0.5 (10% to 50%) or primary tumour G1-2, T1-2, cN0, no LVI, surveillance is an acceptable management option, provided the patient is fully informed of all the risks, and is willing and able to comply with strict surveillance. [97]

Sentinel node biopsy (conventional or dynamic) or limited (modified) ILND should be an alternative option if patient does not willing to comply.[74,97] In the high risk group (nomogram probability more than 0.5 (50%) or primary tumour G3 or T2-4 or cN1-2,or with LVI), complete (radical) ILND should be performed bilaterally, because early ILND (at initial presentation) leads to higher survival rates compared with delayed ILND when groin metastases become palpable during follow-up.[74]

Dynamic sentinel node biopsy (DSNB) is a technique based on the assumption that primary lymphatic drainage from a penile cancer goes to only one inguinal lymph node on each side which may however be in different locations based on individual anatomy. Tc99m nanocolloid is usually injected around the penile cancer site the day before surgery, and additionally patent blue can also be injected before surgery. Further, a gamma-ray detection probe is used intraoperatively for the detection of the sentinel node which is possible in 97% of cases. The protocol has been standardized for routine use and the learning curve is relatively short.[31]

Modified inguinal lymphadenectomy (mILND) is the standard surgical approach in this situation and defines a limited template whereby the superficial inguinal lymph nodes from at least the central and both superior Daseler's zones (cf. Figure 1.1) are removed bilaterally and the greater saphenous vein is left in place.[43,44] The false-negative rate of this approach is between 15-30% and conversion to an ipsilateral radical inguinal lymphadenectomy with complete removal all superficial and deep ILNs is required in the setting of positive inguinal metastatic disease on frozen section.[46,102]

Several studies have emphasised that early inguinal lymphadenectomy in clinically node-negative patients is far superior concerning long-term patient survival compared to therapeutic lymphadenectomy when regional nodal recurrence occurs.[47,37] One prospective study comparing bilateral lymphadenectomy, radiotherapy and surveillance in clinically node-negative patients reported that 5-year overall survival was significantly better with inguinal lymphadenectomy compared to immediate inguinal radiotherapy or that observed with a surveillance strategy (74% vs 66% and 63%, respectively).[48]
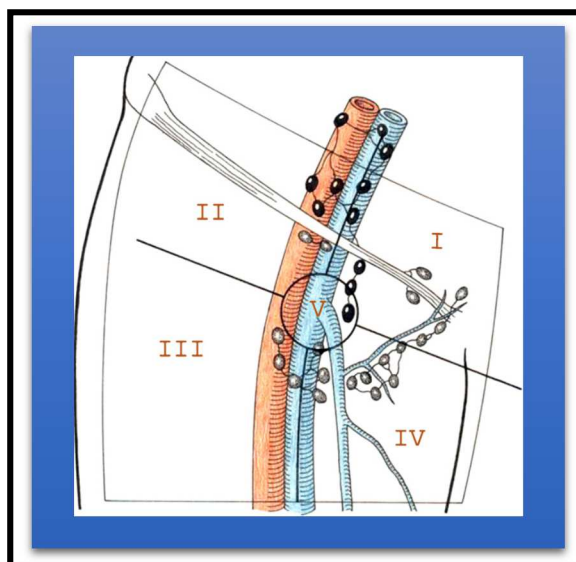
FIGURE 1.1: **LYMPH DRAINAGE REGIONS OF THE INGUINO-FEMORAL REGION (SELER** *et al.)*[43]

The region is divided into five zones: one central zone (v), superior (i) and inferior (iv) medial zones, and superior (ii) and inferior (iii) ateral zones.

1.4.1.2 *Palpable inguinal node*

In recent studies 43% of palpable nodes are positive for malignancy making a 4 to 6 week waiting period an unnecessary delay.[49-51] Thus, this practice is no longer advocated as a tool to select patients who either should or should not undergo lymphadenectomy. To accomplish diagnosis with a positive value of about 70-80%, FNAC has to employed.[52] In patients with cyto- or histologically proven inguinal node metastases which are considered to be surgically resectable, a complete (radical) inguinal node dissection should be performed ipsilaterally, because this may be curative.[34] DSNB is not reliable in patients with palpable and suspected inguinal nodes and should not be used.[53]

1.5 PELVIC NODE

Lymphatic drainage from the primary penile tumour typically follows a systemic pattern. Involvement of the pelvic lymph nodes is not expected in the absence of inguinal lymph node involvement.[33]

The ipsilateral pelvic LND is recommended when node of Cloquet is positive, two or more inguinal nodes are involved and least one node with extracapsular extension.[54] The boundaries of PLND include the iliac bifurcation proximally, ilioinguinal nerve laterally, and the obturator nerve medially. PNLD involves removal of the obturator, internal iliac, and

external iliac LNs as well as any clinically positive LNs in the pelvis. Ipsilateral PLND may be performed in the same operative setting as that of ILND or in a delayed fashion. [33]

PLND is indicated only for bilateral inguinal LN involvement, and it can be performed through a midline suprapubic extra-peritoneal excision.[47] The rate of positive pelvic nodes was found to be 23% in cases with more than two positive inguinal nodes, and 56% for those with more than three positive inguinal nodes, or if there was extra capsular involvement in at least one inguinal node .[37] In the presence of positive pelvic nodes 5 year survival is also decreased to 14% .[55]

1.6   SURGICAL TECHNIQUES OF RADICAL LND AND MODIFIED LND

In patients with clinically positive inguinal disease, radical ILND is recommended for complete surgical staging and treatment. According to Swan *et al.*, boundaries of dissection typically include the following: inguinal ligament and spermatic cord superiorly, the adductor longus muscle medially, and the sartorius muscle laterally.[56] It should be noted that radical ILND is performed from the superior boundary of the aponeurosis of the external oblique and the spermatic cord down, to the inferior border of the inguinal ligament. The dissection is performed down through the fascia lata overlying the Sartorius muscle laterally and medially through the fasica overlying the adductor longus muscle. Dissection is performed superiorly along the femoral artery and vein until the femoral canal is reached. The long saphenous vein is identified within the femoral triangle where it is ligated at the level of the saphenofemoral junction. The Sartorius muscle can then be transposed once ILND is complete by releasing its attachments from the anterior superior iliac spine, providing myocutaneous coverage over the femoral vessels. A closed-suction drain is placed, and the skin is closed with the muscle and subcutaneous tissues reapproximated to obliterate any potential dead space for a postoperative fluid collection that may serve as a nidus for infection or lymphocele formation.[65]

A modified inguinal lymph node dissection (ILND) is primarily done to avoid the morbidity associated with a standard radical ILND. The standard ILND involves sacrificing the saphenous vein, transposing the Sartorius muscle, has an increased risk of lymphoedema and skin necrosis. A modified ILND consists of a shorter skin incision, no dissection lateral to the femoral artery or caudal to the fossa ovalis, preservation of the saphenous vein, and no transposition of the Sartorius muscle.[20,41] This modified technique was described by Catalona in 1988 and decreased complication rates in full nodal dissections from 50% (initially reported by Dassler) to 22% was observed.[21,43,57] More importantly than the

landmarks are the subtleties of the procedure. These include maintaining Camper's fascia, use of skin hooks to elevate the skin flaps leaving the superficial globular fat in place, and careful clipping of all lymphatics to avoid lymph drainage.[22,42] Modified ILND can be performed with frozen section examination of the specimen, and if positive the procedure can converted to extended ILND or ilioinguinal LND.[11,58,59,60,61]

1.7 COMPLICATIONS OF INGUINAL LYMPH NODE DISSECTIONS

The most common complications of inguinal lymph node dissection include infection, seromas, skin necrosis, wound breakdown, lymphorrhoea, chronic leg oedema, deep vein thrombosis (DVT), femoral neuropraxia, and even death.[62.63] Undoubtedly, the technique of modified inguinal lymphadenectomy has resulted in a markedly decreased rate of complications. But, inguinal lymphadenectomy remains a procedure that is prone to local complications and should be performed with care and diligent tissue handling.

The reported incidence of early postoperative wound complications following lymph node dissection varies strongly in the current literature but can be as high as 77%.[64-69] Reported short-term surgical complications include wound infection, seroma formation, skin-flap problems, and wound breakdown.[70] Strategies employed to minimize morbidity include aggressive wound care, minimal intraoperative flap handling, preservation of robust subcutaneous tissue, early ambulation (or, conversely, bed rest in some centres), use of compression stockings, wound drains, antibiotic coverage and appropriate use of myocutaneous flap coverage.[71,72]

Untreated metastatic inguinal and pelvic lymph nodes are usually the cause of death in penile cancer due to infection, ulceration and haemorrhage from femoral vessels.[75.76] Missing the opportunity to surgically cure a patient of metastatic cancer to the inguinal nodes will have catastrophic results with patient survival limited to less than 2 years. Offering patients lymphadenectomy simultaneously with surgery of the primary lesion requires an accurate grading of the lesion preoperatively, and may need an intraoperative frozen section to stage the lesion as T2 or higher, if the cancer is grade 1, for patients to comply with EUA guidelines. In addition, bilateral lymphadenectomy may affect the healing of primary lesion due to lymphoedema or infection.[77] ILND is carried out simultaneously with the removal of the primary tumour or as an elective procedure. In cases of pelvic lymph node involvement or in patients at high risk for pelvic involvement, simultaneous pelvic lymph node dissection (PLND) is performed.[70]

Recently many authors reported that simultaneous lymphadenectomy with primary penile surgery was associated with less morbidity. d`Ancona *et al.* reported on 26 patients who underwent penectomy and bilateral modified ILND concurrently, with no increased complications.[78] Theron and Heyns reported that penectomy and simultaneous lateral radical ILND in the cohort of 18 patients with stage T2-T3 primary lesions and palpable inguinal nodes were not associated with higher complications rates compared with ILND deferred for 10 weeks after surgery. [79]

Thyavihally *et al.* reported on 138 patients who underwent penectomy and simultaneous lymphadenectomy bilateral superficial INLD in 25 (18%) patients, bilateral ilio-inguinal dissection in 86 (62%) and unilateral ilio-inguinal and opposite side superficial ILND in 27 (20%) patients. These authors concluded that ILND can be safely done along with penectomy without increased wound related morbidity and waiting for 3 to 4 weeks in a proven inguinal nodal metastasis may not be necessary in selected cases especially in their country where many patients fail to follow-up after primary surgery.[80] A modified procedure with limited dissection and sparing of the greater saphenous vein in patients with penile carcinoma has been associated with a morbidity rate of 7%.[81]

1.8   INTRODUCTION AND AIM OF THE STUDY

In South Africa, the treatment of penile cancer is not centralized and patients are treated at different health facilities throughout the country. To date, there is limited data on surgical management of penile cancer in South Africa. Most patients treated in our centre are from a low socio-economic background and live in remote areas. These are some of the contributing factors that lead to a loss of follow-up in patients after primary penile surgery. If these patients are put on a surveillance protocol it can lead to progression and morbidity/mortality.

1.8.1   Aim of this study

i.   To describe the profile (Age and HIV status) of men with penile cancer and compare it to the published literature

ii.   To evaluate the incidence of positive lymph nodes and the early complication rate of patients undergoing simultaneous inguinal lymph node dissection (ILND) during surgery for penile carcinoma and

iii.   To describe the incidence of the different histological subtypes found at the Free State Academic Complex.

CHAPTER 2

METHODOLOGY

2.1 STUDY DESIGN

This retrospective descriptive study was conducted following approval from our Institutional Ethics Review Board. Medical records on all consecutive patients who underwent surgery for penile cancer between 2005 and 2015 were obtained from our institutional penile cancer database.

2.1.1 Sample

Files of 41 patients that presented with histologically confirmed penile cancer and underwent surgery for penile cancer during the period between 2005 and 2015 were consecutively reviewed. Patients were identified by utilising the penile cancer database on the Meditech Computer filling system (Free State Academic Complex Computer filing system). The details of the patients were obtained from patients' files kept in the Meditech filling system.

2.1.2 Measurement

The data was collected by the Principle Researcher from the Meditech Computer filing system of the Free State Academic Complex after approval by the Ethics Committee of Faculty of Health Sciences of the University of the Free State.

Histology reports of preoperative penile biopsies and definitive penile and lymph node dissection reports were obtained from the National Health Laboratory Services after a formal request. Information was collected using a preformed questionnaire. The data variables included: Patient demographics (Age and HIV status), pre-operative penile cancer biopsy results, type of surgery performed, and results of the final histology report (histological subtype, tumour stage and grade, site and number of positive inguinal lymph nodes, rate of positive surgical margins and lymphovascular invasion) and early complications of the lymph node dissection.

Patients that presented with a suspicious penile ulcer or mass (cf. Figure 2.1) underwent routine excisional or incisional biopsy to confirm the following:

- To make a histological diagnosis ("African pathology's surprise factor");

- To establish the grading of the tumour, which is necessary when penile preservative treatment is contemplated;

- For risk-adapted strategy in treatment of regional lymph nodes;

- To allow proper counselling; and

- For medico-legal reasons[45]

FIGURE 2.1: A PATIENT THAT PRESENTED WITH A PENILE MASS WHICH WAS HISTOLOGICALLY PROVEN TO BE HERPES ("AFRICAN PATHOLOGY'S SURPRISE FACTOR") AT THE FREE STATE ACADEMIC COMPLEX

All patients that presented with suspicious penile lesions suggestive of penile cancer were taken for routine excisional or incisional biopsy after a complete physical examination that focused on the penile lesion, rest of the penis and inguinal regions for palpable nodes. Fine needle aspiration of palpable inguinal nodes was concurrently performed with biopsy of primary penile lesion based on our Institutional protocol. The decision on the type of surgical intervention to be performed depended on the location of tumour. Tumour and nodal classification was according to the 2009 UICC International Union against Cancer Tumour Node Metastasis stage classification system as summarised in Table 1.1.

2.1.3 Analysis of data

Descriptive statistics namely means and standard deviations or medians and percentiles were calculated for continuous data. Frequencies and percentages were calculated for categorical data. Information obtained from files was transferred to Excel spreadsheet

(Microsoft) for tabulation of data. The statistical analysis was done by the Department of Biostatistics of University of the Free State using the Statistical Analysis System (SAS).

2.2 ETHICAL CONSIDERATIONS

Ethical approval to conduct the study was obtained from the Ethics committee of the Faculty of Health Sciences of the University of the Free State before commencement of the study.

CHAPTER 3

RESULTS

3.1   AGE AND HIV PROFILE

A total of 41 patients that presented with histologically confirmed penile cancer were surgically treated. Table 3.1 demonstrates the age distribution and HIV status of the study cohort. Mean age was 50 years (range 30-86 years). HIV status was known in 20 patients and revealed positive results in 16 patients (80%) while four patients (20%) were HIV negative.

TABLE 3.1: AGE DISTRIBUTION AND HIV STATUS OF THE STUDY POPULATION

Age Group (years)	N of Patients (%)
<19	0 (0)
20-29	0 (0)
30-39	10 (24.4)
40-49	11 (26.8)
50-59	9 (22)
60-69	7 (17)
70-79	3 (7.3)
80-89	1 (2)
≥90	0 (0)
Total	**41 (100)**
HIV status	
Negative	4 (9.8)
Positive	16 (39)
Unavailable	21 (51.2)

3.2   PATHOLOGICAL CHARACTERISTICS OF PENILE CANCER PATIENTS OF THIS STUDY GROUP

The pathology data of the 41 evaluated patients is presented in Table 3.2. Of these 41 patients, penile cancer diagnosis was confirmed by pre-operative histological analysis of biopsy in 30 patients (73.2%), two patients (4.9%) showed benign diagnosis with an aggressive clinical presentation and biopsy results were not found in nine patients (21.9%).

TABLE 3.2: PATHOLOGICAL PROFILE OF THE COHORT

N OF PATIENTS	
1. Pre-operative biopsy	
Malignant	30 (73.2)
Non-malignant	2 (4.9)
Not available	9 (21.9)
2. Pathological T staging	
PTa	2 (80.1)
PTcis	0 (0)
PT2	16 (39)
PT3	8 (19.5)
PT4	1 (2.4)
Not available	5 (12.2)
3. Post-surgical histological subtype	
Classic SCC	34 (83)
CC with spindle cell differentiation	1 (2.4)
Warty cancer	3 (7.3)
Verrucous cancer	3 (7.3)
BCC	0 (0)
Melanoma	0 (0)
Sarcoma	0 (0)
Others	0 (0)
4. Tumour grading	
Grade 1	15 (36.6)
Grade 2	18 (43.9)
Grade 3	5 (12.2)
Grade 4	0 (0)
Not available	3 (7.3)

According to AJCC 2009 classification, T2 pathological staging of primary penile tumour contributed to majority of the patients (39%). All of the 41 patients were diagnosed with squamous cell carcinoma (SCC), the predominant histological subtype was presented as classic squamous cell carcinoma in 34 patients (83%). This was followed by warty cancer subtype in three patients (7.3%), verrucous subtype in three patients (7.3%); and a poorly differentiated SCC with spindle cell component occurred in one patient (2.4%).

The three patients with warty cancer and other three patients with verrucous histological subtypes had Ta and T1 pathological staging. The penile tumour grading was well differentiated (G1) in 15 patients (36.6%), moderately differentiated (G2) in 18 patients (43.9%), poorly differentiated in five patients (12.2%) and in three patients (7.3 %) tumour differentiation was not reported.

Twenty-five patients underwent lymph node dissection for clinically palpable nodes or higher grade pT1 disease or higher. Of these patients, eight patients (32%) had lymph node metastasis and no lymph node metastases were detected in the remaining 17 patients

(68%). Of the eight patients (32%) who showed positive nodal metastasis, five patients had positive unilateral groin nodes and three had bilateral groin involvement. Table 3.3 describes the characteristics of eight patients with nodal metastasis according to staging, grading and lymphovascular invasion. This table depicts higher pathological staging and grading associated with the presence of nodal metastasis.

TABLE 3.3: CHARACTERISTICS OF EIGHT PATIENTS WITH NODAL METASTASIS

N OF PATIENTS (%)	
1. Stage	
T1	1
T2	3
T3	4
2. Histological grading	
G1 (well differentiated)	1
G2 (moderate differentiated)	5
G3 (poor differentiated)	2
3. Lymphovascular invasion	
Yes	3
No	1
Not reported	4

Of the study population, seven of the 41 patients (17.1%) had LVI, eight patients (19.5%) tested negative for LVI and in 26 patients (63.4%) LVI was not reported.

3.3   SURGICAL PROCEDURES

All 41 patients underwent surgical procedures as demonstrated in Table 3.4. According to the results partial penectomy was the predominant surgical procedure performed accounting for 58.5% of the patients. This was followed by a relative number of 14 patients (34.2%) who experienced total penectomy for cT3 and cT4 disease, and two patients (4.9%) underwent glansectomy. Unfortunately surgical procedure was not clearly stated in one patient (2.4%).

TABLE 3.4: SURGICAL PROCEDURES

N of Patients (%)	
Type of surgery	
Glansectomy	2 (4.9)
Partial penectomy	24 (58.5)
Total penectomy	14 (34.2)
Not available	1 (2.4)
Pathological n stage	
Pn0	7 (41.5)
Pn1	4 (9.8)
Pn2	4 (9.8)

Pn3	0 (0)
Not available	16 (39)
Perfomance of LnD	
No	16 (39)
Yes	25 (60.9)
Unilateral	0
Bilateral	25
Radical ILND	0
Modified ILND	25
Site of pathological involvement	
Unilateral	4 (9.8)
Bilateral	4 (9.8)
None	17 (41.5)
Not done	16 (39)
Surgical margins	
Positive	5 (12.2)
Negative	28 (68.3)
Not available	8 (19.5)
Lymphovascular invasion	
Positive	7 (17.1)
Negative	8 (19.5)
Not available	26 (63.4)

Figure 3.1 shows a penis with penile cancer preoperatively, while Figure 3.2 show a penis of the same patient after partial penectomy.

FIGURE 3.1: PATIENT THAT PRESENTED WITH A LARGE PENILE MASS AT THE FREE STATE ACADEMIC COMPLEX

FIGURE 3.2: COSMETIC OUTCOMES AFTER PARTIAL PENECTOMY PERFORMED ON THE SAME PATIENT SHOWN IN FIGURE 3.1

3.4   EARLY LYMPH NODE DISSECTION COMPLICATIONS

Twenty-five patients had simultaneous primary penile surgery in the form of glansectomy, partial or total penectomy with perineal urethrostomy and modified inguinal lymph node dissection (cf. Table 3.5). Complications associated with simultaneous penile surgery and lymph node dissection were seromas in two patients (8%), one superficial wound infection (4%) and 17 patients (68%) did not have post-operative complications. Five patients (20%) were lost to follow-up postoperatively. Of note, there were nine patients with HPV positive histology either in primary tumour or dissected lymph nodes. Of these nine patients, four patients were HIV positive (aged 32, 35, 37 and 47) and the remaining five patients' HIV status was not recorded in the database.

TABLE 3.5: POST-OPERATIVE COMPLICATIONS FOLLOWING SIMULTANEOUS PENILE AND NODAL SURGERIES

	Frequency %	Post-operative complications
Wound infections	1	4
Hematoma	0	0
Seroma	2	8
Lymphedema	0	0
Pain	0	0
None	17	68
Other (lost to follow-up)	5	20

CHAPTER 4

CONCLUSIONS AND RECOMMENDATIONS

4.1 CONCLUSIONS

Cancer of the penis, although rare in developed countries, continuous to be a challenge to the urologist practising in the developing countries such as South Africa, where the frequency of this malignancy is as high as 10-20% of all male cancers.[3,82]

Penile cancer may occur at any age although most common in elderly people with peak incidence around the 6th and 7th decades in the developed countries.[8] On the contrary this study revealed that the median age was 50 years and the majority of patients were less than the age of 50 years and accounting account for 50% of the overall study group. This finding is confirmed by other African literature studies.[82-88] Chalya *et al.* (2015) from Tanzania also reported that in his cohort of 236 the median age of their study group was 47 years which is a younger age than described in most literature from developed countries.[89] Additionally, Chen *et al.* (2012) from Beijing discovered that the median age of his study group was 51.2 years in the cohort of 93 patients.[90] Furthermore Koifman *et al.* also assessed 230 patients retrospectively in Rio de Janeiro (Brazil) and the youngest four patients were between 2nd and 3rd decade of life.[91]

Infection with HIV, the virus that causes Acquired Immuno-Deficiency Syndrome (AIDS), is major a risk factor for penile cancer. An estimated 70% of HIV positive men acquired the virus through vaginal intercourse, and in Africa this figure is >90%.[96] Penile cancer is increased 8-fold in individuals affected by HIV, the reason for this observation is not fully understood and may be due to increased incidence of HPV infection.[92] In this particular study, HIV status was known in 20 patients, out of these 16 patients (80%) were found to be HIV positive. The overall HIV positive prevalence was significantly higher in our study. This is in agreement with UNAIDS which stated that Sub-Saharan Africa is the region worst-affected by HIV and AIDS. It has been established that South Africa has the highest prevalence of HIV/AIDS compared to any other country in the world with 5,6 million people living with HIV, and 270,000 HIV related deaths were recorded in 2011.[93]

Penile SCC is commonly characterized by lymph node spread in a stepwise pattern before distant metastases. The incidence of palpable inguinal lymph nodes at the time of initial presentation is reported as 30-60%.[53] In our study the incidence of palpable nodes at initial

presentation was 61%, and this correlates (well) with the above mentioned study. The incidence of micro metastases to the lymph nodes has been reported to be as high as 50% in clinically palpable nodes and up to 24% in clinically impalpable nodes.[49,51,94] In the present study of 41 patients, 25 patients (61%) had clinically palpable nodes at presentation and underwent modified ILND. Of these 25 patients, eight patients (32%) had nodal metastasis which correlates with the abovementioned published literature and 17 patients (68%) did not have nodal metastasis. Sixteen patients did not undergo lymph node dissection due to various reasons such as resolution of palpable nodes six weeks after completion of prophylactic antibiotics, or lost to follow-up after primary penile surgery or surveillance in node negative patients. From 2010, we discontinued the use of prophylactic antibiotics to discern between the inflammatory and malignant nodes. Prophylactic antibiotics are now only used during the peri-operative period.

Success in the management of penile cancer depends entirely on the timely and appropriate management of the inguinal and pelvic lymph nodes. The most important and controversial area in the treatment of treating penile cancer is the management of clinically non-palpable groin nodes. The prophylactic inguinal lymphadenectomy has shown improved survival in patients with microscopic metastasis in comparison to those who had negative nodes initially, and developed nodal recurrence at follow-up. Prophylactic inguinal lymphadenectomy can be curative in 20% to 60% of histologically node-positive patients.[22,59]

Recent evidence demonstrates improved survival outcomes without increased morbidity with early inguinal lymph node dissection when compared to delayed dissection.[39-41] Early reports of penectomy and simultaneous bilateral ilioinguinal LND for carcinoma of the penis were associated with many complications, resulting in the modification of the procedure so that the primary tumour was removed first and LND was performed weeks later.[37-38] Subsequently several studies have indicated that there is no increased complication rate with concurrent bilateral ILND at the time of penectomy, as long as proper preoperative antibiotics are given and standard postoperative care followed.[42-44] In our cohort, only two patients (8%) had seromas and were treated with aspiration, a course of antibiotics and surveillance. One patient (4%) had a superficial wound infection which was treated with oral antibiotics and resolved successfully. The overall early post lymph node dissection complication rate was 12% in the present study. Our study confirms that simultaneous primary penile surgery and inguinal lymph node dissection is not associated with increased postoperative complications. On the contrary, recent large series from centres with high volume of patients showed that overall complication rates can be as high as 90% as

observed in Table 4.1. If compared to our series the authors discovered that the overall complication rates were high. However, all these large series included patients who underwent modified and/or extended ILND and did not attempt to separate complication rates of superficial and deep ILND; which can explain higher complications rates if compared to our where all patients had a modified ILND.

In many centres, elective inguinal lymph node dissection remains the standard treatment for management of moderately and poorly differentiated penile carcinoma in the presence of clinically negative inguinal nodes. However, this unnecessarily exposes up to 80% of patients to significant morbidity. While some advocate surveillance of the inguinal nodes, this patient population has a high non-compliance rate and many may be lost to follow-up until they present much later with gross inguinal or terminal disease.

In our centre, the management of clinically palpable nodes entails: Fine needle aspiration cytology (FNAC) for all patients will palpable lymph node (LN) initially. Unilateral or Bilateral therapeutic radical ILND is done if FNAC is positive. In the case of an Unilateral positive FNAC, unilateral modified radical ILND is done with contralateral limited ILND with frozen sections (FZ) and complete ILND is done if FZ is positive. In all other patients: a limited/modified ILND with FZ is done and a complete ILND is only performed if FZ is positive. Pelvic lymphadenectomy is done at a later stage if: More than 2 nodes positive, Grade 3/4 tumor in nodes, extra nodular extension (ENE) and positive Cloquet node[.45]

TABLE 4.1: COMPLICATIONS POST-SURGERY

	Pts	Overall Complication	% Wound infection	Seroma%	Lymphocele%	Lymphodema
Ornellas *et al.*(98)	170	20.6	0.6	12.4	2	4.1
Stuvier *et al.* (70)	163	58	43	2.4	-	-
Ravi (99)	112	84	18	5	9	25
Lopes *et al.* (100)	145	89.7	-	-	30	29.1
Gopman *et al.*(101)	327	55.4	31.5	26.5	7.6	-
Current	25	12	4	8	-	-

Management of clinically non-palpable nodes: risk stratification based on histological grading of primary tumour, sonar guided fine needle aspiration and DSND biopsy (which is not readily available).

Squamous cell carcinoma accounts for more than 95% of cases of malignant diseases of the penis. Although SCC is the most common penile neoplasia, distinct different histological types with varying growth patterns, clinical aggressiveness and HPV association have been identified.[49] The frequency of histological subtypes according to EAU guidelines are as follows: common SCC 48-65%, basaloid carcinoma 4-10%, warty carcinoma 7-10%, verrucous carcinoma 3-8%, papillary carcinoma 5-15%, sarcomatoid carcinoma 1-3% and mixed carcinoma 9-10.[49] In our study, we discovered classic SCC as the major histological subtype (83%). This is higher compared to EAU guidelines, while verrucous and warty cancer were observed in minimal numbers (both 7.3%). Verrucous and warty cancer were associated with low grade and superficial invasion, none of these tumours were T2 in pathological staging. This is typical behaviour of these tumours and also associated with higher 10 year survival rate for verrucous and warty cancers (100 and 90% respectively).[50]

South Africa is a 3rd world country where the majority of people are of low socio-economic background and live far away from major cities. These patients do not return regularly for follow-up especially after primary penile surgery and if on a surveillance protocol this can lead to progression and morbidity/mortality.[21,79] Non-compliance is multifaceted in South Africa, due to transport from remote areas to the cities, lack of education or cultural background and beliefs. Despite extensive counselling about the importance of follow-up and emphasizing the fact that prognosis depend on the nodal status, many patients think that the radical and emasculating penile surgery was their definitive treatment.[79]

From this study, simultaneous primary penile surgery and lymph node dissection was not associated with increased early postoperative complications even in HIV positive patients, which are at higher risk of various infections depending on CD4 count and viral loads. CD4 counts of <500/mm^3 are associated with opportunistic infections and certain malignancies, so-called 'AIDS-defining' conditions.[96]

Early age at presentation with penile cancer was noted during our research and this is supported by published literature. Despite the high incidence of HIV in this cohort and the supporting literature stating that HIV positive patients are at higher risk of penile cancer, the reason for the early age at presentation could not be clarified. Therefore, further studies need to be conducted to confirm that HIV can contribute to the development of penile cancer at a younger age than seen in previous published literature, especially among people of African origin. About 15% of HIV-seropositive patients and 30–50% of patients with AIDS, develop a cancer especially Kaposi Sarcoma and Non Hodgkin lymphoma.[95] However, we should report that these tumours were not observed in the current cohort. This could be due

to various reasons such as high CD4 count at presentation and/or patients already treated with highly active antiretroviral therapy (HAART).

The potential limitation of this study is the limited number of patients and retrospective nature. However, the data in this study will assist healthcare professionals in the management of patients with penile carcinoma and can also be used as a foundation for prospective studies.

4.2   RECOMMENDATIONS

Early age at presentation and a high incidence of HIV was observed in the present study which shows a similar trend than other published studies. Simultaneous primary penile surgery and inguinal lymphadenectomy can be done safely in a population with a high incidence of infection and HIV-associated lymphadenopathy. In our setting, where non-compliance and lost to follow-up rates are high, simultaneous primary penile and lymph node dissection is advisable, but the importance of serial follow-up for recurrences and distal metastases cannot be ignored. There was a high incidence of node negative ILND in the current study. Penile cancer histological subtypes correlates with published literature despite high prevalence of HIV infection.

In South Africa penile cancer remains a serious challenge to the urologists treating this malignancy due to absence of centres of excellence which leads to non-standardized protocols. Additionally, the minimal number of patients treated throughout this country contributes to the limited research in this field. Therefore, if these challenges can be overcome it could lead to improvements in the treatment of this relatively rare cancer in South Africa.

REFERENCES

1. Siegel, R., Naishadham, D., Jemal, A. 2012. Cancer statistics, 2012. *A Cancer Journal for Clinicians.* 62(1):10-29.

2. Misra, S., Chaturvedi, A., Misra, N.C. 2004. Penile carcinoma: a challenge for the developing world. *Journal of Lancet Oncology.* 5(4):240-247.

3. Bleeker, M.C., Heideman, D.A., Snijders, P.J., Horenblas, S., Dillner, J., Meijer, C.J. 2009. Penile cancer: epidemiology, pathogenesis and prevention. *World Journal of Urology.* 27(2):141-150.

4. Dillner, J., Von Krogh, G., Horenblas, S., Meijer, C.J. 2000. Etiology of squamous cell carcinoma of the penis. *Scandinavian Journal of Urology and Nephrology.* 205:189–193.

5. Daling, J.R., Madeleine, M.M., Johnson, L.G., Schwartz, S.M., Shera, K.A., Wurscher, M.A., Carter, J.J., Porter, P.L., Galloway, D.A., McDougall, J.K., Krieger, J.N. 2005. Penile cancer: importance of circumcision, human papillomavirus and smoking in situ and invasive disease. *International Journal of Cancer.* 116(4):606-616.

6. Pizzocaro, G., Algaba, F., Horenblas, S., Solsona, E., Tana, S., Van der Poel, Watkin, N.A. 2010. EAU Penile cancer guidelines 2009. *Journal of European Urology.* 1002-1012.

7. Cubilla, A.L., Reuter, V., Velazquez, E., Piris, A., Saito, S., Young, R.H. 2001. Histologic classification of penile carcinoma and its relation to outcome in 61 patients with primary resection. *International Journal of Surgical Pathology.* 9:111-120.

8. Salvioni, R., Necchi, A., Piva, L., Colecchia, M., Nicolai, N. 2009. Penile cancer. *Journal of Urologic Oncology.* 27:677-685.

9. Rubin, M.A., Kleter, B., Zhou, M., Ayala, G., Cubilla, A.L., Quint, W.G.V., Pirog, E.C. 2001. Detection and typing of human papilloma virus DNA in penile carcinoma: evidence of multiple pathways of penile carcinogenesis. *The American Journal of Pathology.* 159(4):1211-1218.

10. Moses, K.A., Winer, A., Sfakianos, J.P., Poon, S.A., Kent, M., Bernstein, M., Russo, P., Dalbagni, G. 2014. Contemporary Management of penile cancer: Greater than 15 year MSKCC Experience. *The Canadian Journal of Urology.* 21(2):7201-70206.

11. Ornellas, A.A., Seixas, A.L., Marota, A., Wisnescky, A., Campos, F., De Moaraes. 1994. Surgical treatment of invasive squamous cell carcinoma of the penis: retrospective analysis of 350 cases. *Journal of Urology.* 151:1244-1249.

12. Srinivas, V., Morse, M.J., Herr, H.W., Sogani, P.C., Whitmore, W.F. Jr. 1987. Penile cancer: relation of extent of nodal metastasis to survival. *Journal of Urology.* 137:880-882.

13. Pettaway, C.A., Lynch, D.F., Davis, J.W. 2007. Tumors of the penis. In: Wein AJ, Kavoussi LR, Novick AC, *et al.*, eds. *Campbell-Walsh Urology*, 9th ed, vol. 1. Philadelphia: Saunders Elsevier. 959-992.

14. Saisorn, I., Lawrentschuk, N., Leewansangtong, S., *et al.* 2006. Fine-needle aspiration cytology predicts inguinal lymph node metastasis without antibiotic pretreatment in penile carcinoma. *British Journal of Urology International.* 97:1225-1228.

15. Fraley, E., Zhang, G., Sazama, R., Lange, P.H. 1985. Cancer of the penis: Prognosis and treatment plans. *Journal of Cancer.* 55:1618-1624.

16. Kossow, J.H., Hotchkiss, R.S., Morales, P.A. 1973. Carcinoma of the penis treated surgically: Analysis of 100 cases. *Journal of Urology.* 2:169-182.

17. Horenblas, S., Kröger, R., Gallee, M.P., *et al.* 1994. Ultrasound in squamous cell carcinoma of the penis; a useful addition to clinical staging? A comparison of ultrasound with histopathology. *Journal of Urology.* 43:702-7.

18. Richter, S., Ruether, D.J., Canil, C., Moretto, P., *et al.* 2013. Management of carcinoma of the penis: Consensus statement from the Canadian Association of Genitourinary Medical Oncologists (CAGMO)*. Canadian Urological Association Journal.* 7(11-12):797-811.

19. Hegarty, P.K., Dinney, C.P., Pettaway CA. 2010. Controversies in Ilioinguinal lymphadenectomy. *Urologic Clinics of North America.* 37:421-434.

20. Deem, S., Keane, T., Bhavsar, R., El-Zawahary, A., Savage, S. 2011. Contemporary diagnosis and management of squamous cell carcinoma (SCC) of the penis. *British Journal of Urology International.* 108:1378-92.

21. Yeung, L.L., Brandes, S.B. 2013. Dynamic sentinel lymph node biopsy as the new paradigm for the management of penile cancer*. Urologic Oncology: Seminars and Original Investigations.* 31: 693-696.

22. Tabatabaei, S., McDougal, W.S. 2010. Inguinal lymphadenectomy for penile carcinoma. In: Graham SD Jr., Keane TE eds. *Glenn's Urologic Surgery*, 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins. 473-80.

23. Bamholtz-sloan, J.S., Maldonalo, J.L, Pow-sang, J., *et al.* 2007. Incidence trends in primary malignant penile cancer. *Urologic Oncology.* 25:361-367.

24. Heyns, C.F., Mendoza-valdes, A., Pompeo, A.C. 2010. Diagnosis and staging of penile cancer. *Journal of Urology.* 76:15-23.

25. Burgers, J.K., Badalament, R.A., Drago, J.R. 1992. Penile cancer. Clinical presentation diagnosis, and staging. *Urologic Clinics of North America.*19:247-256.

26. Van Poppel, H., Watkin, N.A., *et al.* Penile cancer: 2013. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 00:1-10.

27. Hakenberg, O.W., *et al.* 2015. Guidelines on penile cancer. *Journal of European Urology.* 67(1):142-50.

28. Busby, E.J., Pettaway, C.A. 2005. What`s new in the management of penile cancer?. *Current Opinion in Urology.* 15:350-357.

29. Graafland, N.M., Teertstra, H.J., Besnard, A.P., *et al.* 2011. Identification of high risk pathological node positive penile carcinoma: value of preoperative computerized tomography imaging. *Journal of Urology.* 185(3):881-887.

30. Lont, A.P., Kroon, B.K., Gallee, M.P. *et al.* 2007. Pelvic lymph node dissection for penile carcinoma: extent of inguinal node involvement as an indicator for pelvic node involvement and survival. *Journal of Urology.* 177(3):947-952.

31. Leijte, J.A., Hughes, B., Graafland, N.M. *et al.* 2009. Two-center evaluation of dynamic sentinel node biopsy for squamous cell carcinoma of the penis*. Journal of Clinical Oncology.* 27:3325-3329.

32. Leijtie, J.A., Kroon, B.K., Valdes Olmos, R.A., Nieweg, O.E., Horenblas, S. 2007. Reliability and safety of current dynamic sentinel node biopsy for penile carcinoma. Journal of European Urology. 52(1):170-177.

33. Sharma, P., Zargar-Shoshtari, K., Spies, E.P. 2015. Current surgical management of penile cancer. *Current Problems in Cancer.* 39:147-157.

34. *National Comprehensive Cancer Network.* 2014. Clinical practice guidelines in oncology. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp

35. Hegarty, P.K., Eardley, I. *et al.* 2014. Penile cancer: organ sparing techniques. *British Journal of Urology International.* 114:799-805.

36. Branney, P., Witty, K., Eardley, I. 2011. Patients' experiences of penile cancer. *Journal of European Urology.* 59:959-961.

37. Ornellas, A.A., Kinchin, E.W., No brega, B.L., *et al.* 2008. Surgical treatment of invasive squamous cell carcinoma of the penis: brazilian national cancer institute long-term experience. *Journal of Surgical Oncology.* 97(6):487-95.

38. Philippou, P., Shabbir, M., Malone, P., *et al.* 2012. Conservative surgery for squamous cell carcinoma of the penis: resection margins and long-term oncological control. *Journal of Urology.* 188(3):803-8.

39. Agrawal, A., Pai, D. *et al.* 2000. The histological extent of the local spread of carcinoma of the penis and its therapeutic implications. *British Journal of Urology International.* 85:299-301.

40. Hoffman, M.A., Renshaw, A.A., Loughlin, K.R. 1999. Squamous cell carcinoma of the penis and microscopic pathologic margins. How much margins is needed for local cure? *Journal of Cancer.*85:1565-8.

41. Bissada, N.K., Yakout, H.H., Fahmy, W.E., *et al.* 2003. Multi-institutional long-term experience with conservative surgery for invasive penile carcinoma. *Journal of Urology.* 169 (2):500-502.

42. Garaffa, G., Raheem, A.A., Christopher, N.A., Ralph, D.J. 2009. Total phallic reconstruction after penile amputation for carcinoma. *British Journal of Urology International.*104(6):852-856.

43. Daseler, E.H., Anson, B.J., Reimann, A.F. 1948. Radical excision of inguinal and iliac lymph glands: a study based upon 450 anatomical dissections and upon supportive clinical observations. *The Journal of surgery, gynecology and obstetrics.* 87(6):679-94.

44. Horenblas, S. 2001. Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: the role and technique of lymph node dissection. *British Journal of Urology International.* 88(5):473-83.

45. Wentzel, S.W., Vermeulen, L.P., Otto, J.H. The management of penile carcinoma at Universitas Hospital Urology department, Bloemfontein. 2011 unpublished.

46. Lopes, A., Rossi, B.M., Fonseca, F.P., Morini, S. 1996. Unreliability of modified lymphadenectomy for clinical staging of penile cancer. *Journal of Cancer.* 77(10):2099-2102.

47. Leijte, J.A., Kirrander, P., Antonini, N., *et al.* 2008. Recurrence patterns of squamous cell carcinoma of the penis: recommendations for follow-up based on a two-centre analysis of 700 patients. *Journal of European Urology.* 54(1):161-168.

48. Kulkarni, J.N., Kamat, M.R. 1994. Prophylactic bilateral groin node dissection versus prophylactic radiotherapy and surveillance in patients with N0 and N1-2A carcinoma of the penis. *Journal of European Urology.* 26(2):123-128.

49. Kroon, B.K., Horenblas, S., Deurloo, E.E., *et al.* 2005. Ultrasonography guided Fine-needle aspiration cytology before sentinel node biopsy in patients with penile carcinoma. *British Journal of Urology International.* 95:517-521.

50. Kroon, B.K., Horenblas, S., Estourgie, S.H., *et al.* 2004. How to avoid false-negative dynamic sentinel node procedures in penile carcinoma [see comment]. *Journal of Urology.* 171(1):2191-2194.

51. Kroon, B.K., Horenblas, S., Lont, A.P., *et al.* 2005. Patients with penile carcinoma benefit from immediate resection of clinically occult lymph node metastases. *Journal of Urology.* 173:816-819.

52. Horenblas, S., Tinteren, H., Delemarre, J.F., *et al.* 1991. Squamous cell carcinoma of the penis: accuracy of tumour, nodes and metastases classification system and role of lymphangiography, computerized tomography scan, and fine needle aspiration cytology. *Journal of urology.* 146:1279-83.

53. Horenblas, S. 2001. Lymphadenectomy for squamous cell carcinoma of the penis. Part1: diagnosis of lymph node metastasis. *British Journal of Urology International*. 88: 467-72.

54. Liu, J.Y., Li, Y.H., Zhang, Z.L., *et al*. 2013. The risk factors for the presence of pelvic node mestastasis in penile squamous cell carcinoma patients with lymph node dissection. *World Journal of Urology*. 31(6):1519-1524.

55. Pettaway, C.A., Lance, R.S., Davis, J.W. 2012. Tumours of the penis. In: Wein AJ (editor*). Campbell-Walsh Urology*. Philadelphia: Elsevier-Saunders. 901-933.

56. Swan, M.C., Furniss, D., Cassell, O.C. 2004. Surgical management of metastatic inguinal lymphadenopathy. *British Medical Journal.* 329 (7477):1272-1276.

57. Graafland, N.M., Leitjie, J.A., Olmos, R.A. *et al*. 2010. Repeat dynamic sentinel node biopsy in locally recurrent penile carcinoma. *British Journal of Urology International*. 105:1121-1124.

58. Ravi, R., Shrivastava, B.R., Mallikarjuna, V.S. 1991. Inguinal pick in invasive penile carcinoma: can it stage node negative patients? *Archivos Españoles de Urología*. 44:1123-1126.

59. McDougal, W.S., Kirchner, F.K. (Jr), Edwards, R.H., *et al*. 1986. Treatment of carcinoma of the penis: the case for primary lymphadenectomy. *Journal of Urology*.136:38-41.

60. Sánchez-Ortiz, R.F., Pettaway, C.A. 2004. The role of lymphadenectomy in penile cancer. Journal of *Urological Oncology*. 22:236-245.

61. Siow, W.Y., Cheng, C. 2005. Penile cancer: current challenges. *The Canadian Journal of Urology.* 12(1):18-23.

62. Theodorescu, D., Russo, P., Zhang, Z.F., Morash, C., Fair, W.R. 1996. Outcomes of initial surveillance of invasive squamous cell carcinoma of the penis and negative nodes. *Journal of Urology*. 155:1626-31.

63. Lindegaard, J.C., Nielsen, O.S., Lundbeck, F.A., Mamsen, A., Studstrup, H.N., Von der Maase, H.A. 1996. Retrospective analysis of 82 cases of cancer of the penis. *British journal of urology.* 77:883-890.

64. Poos, H.P., Kruijff, S., Bastiaannet, E., Van Ginkel, R.J., Hoekstra, H.J. 2009. Therapeutic groin dissection for melanoma: risk factors for short term morbidity. *European Journal of Surgical Oncology.* 35:877-883.

65. Spiess, P.E., Hernandez, M.S., Pettaway, C.A. 2008. Contemporary inguinal lymph node dissection: minimizing complications. *World Journal of Urology*. 27:205-212.

66. Gould, N. 2001. Predictors of complications after inguinal lymphadenectomy. *Gynecologic Oncology*. 82:329-332.

67. Gaarenstroom, K.N., Kenter, G.G., Trimbos, J.B., *et al.* 2003. Postoperative complications after vulvectomy and inguinofemoral lymphadenectomy using separate groin incisions. *International Journal of Gynaecology Cancer*. 13: 522-527.

68. Serpell, J.W., Carne, P.W.G., Bailey, M. 2003. Radical lymph node dissection for melanoma. *ANZ Journal of Surgery*. 73:294-299.

69. Ercole, C.E., Pow-Sang, J.M., Spiess, P.E. 2013. Update in the surgical principles and therapeutic outcomes of inguinal lymph node dissection for penile cancer. *Journal of Urologic Oncology*. 31:505-516.

70. Stuiver, M.M., Djajadiningrat, R.S., Graafland, N.M., Vincent, A.D., Lucas, C., Horenblas, S. 2013. Early Wound Complications after Inguinal Lymphadenectomy in Penile Cancer: A Historical Cohort Study and Risk-factor Analysis. *Journal of European Urology*. 6:486-492.

71. Bevan-Thomas, R., Slaton, J.W., Pettaway, C.A. 2012. Contemporary morbidity from lymphadenectomy for penile squamous cell carcinoma: the M.D. Anderson Cancer Center experience. *Journal of Urology.*167:1638-1642.

72. Nelson, B.A., Cookson, M.S., Smith, J.A. (Jr), *et al.* 2004. Complication of inguinal and pelvic lymphadenctomy for squamous cell carcinoma of the penis: a contemporary series. Journal of Urology. 172:494-497.

73. Crawford, E.D., Daneshgari, F. 1992. Management of regional lymphatic drainage in carcinoma of the penis. *Urologic Clinics of North America*. 19:305-317.

74. Heyns, C.F., Fleshner, N., Sangar, V., *et al.* 2010. Management of the lymph nodes in penile cancer. *Journal of Urology.* 76:S43-57.

75. Pompeo, A.C. 2005. Extended lymphadenectomy in penile cancer*. The Canadian Journal of Urology.* 12 Suppl 1:30-6; discussion: 97-8.

76. Solsona, E., Algaba, F., Horenblas, S., Pizzocaro, G., Windahl. 2004. Guidelines on penile cancer. *Journal of European Urology*. 46(1):1-8.

77. Hegarty, P.K. 2009. Delayed lymphadenectomy in patients with carcinoma of the penis. *Indian journal of Cancer*. Vol. 46, No. 3, July-September, pp.182-183.

78. D 'Ancona, C.A., De Lucena, R.G., Querne, F.A., Martins, M.H., Denardi, F., Netto, N.R. (Jr.). 2004. Long-term followup of penile carcinoma treated with penectomy and bilateral modified inguinal lymphadenectomy. *Journal of Urology.* 172:498-501.

79. Theron, P.D., Heyns, C.F. 2007. Penectomy with simultaneous compared to deferred bilateral inguinal lymph node dissection for squamous cell carcinoma of the penis– evaluation of surgical complications. *African Journal of Urology.* 13(1):8-16.

80. Thyavihally, Y.B.,Tongaonkar, H.B., Sengar, M., Pai, K., Bapat, A. 2008. Simultaneous inguinal lymph node dissection and penile surgery in patients with carcinoma of penis: Assessment of complications. *Indian Journal of Urology*. Suppl 2, Vol.24, ps133.

81. Bouchot, O., Rigaud, J., Maillet, F., Hetet, J.F., Karam, G. 2004. Morbidity of inguinal lymphadenectomy for invasive penile carcinoma. *Journal of European Urology*. 45:761-766.

82. Wabinga, H.R., Parkin, D.M., Wabwire-Mangen, F., Nambooze, S. 2000. Trends in cancer incidence in Kyadondo County, Uganda, 1960-1997. *British Journal of Cancer*. 82:1585-1592.

83. Kyalwazi, S.K. 1966. Carcinoma of the penis: a review of 153 patients admitted to Mulago Hospital, Kampala, Uganda. *East African Medical Journal.* 43:415-425.

84. And, B.D., Kyalwazi, S.K. 1972. Review of carcinoma of penis at Mulago. *East African Medical Journal*. 49:996-1001.

85. Williams, E.H. 1966. A local cancer registry in a mission hospital in Uganda. *East African Medical Journal*. 43:200-207.

86. Elshleman, J.L. 1966. A study of the relative incidence of malignant tumors seen at Shirati Hospital in Tanzania. *East African Medical Journal*. 43:273-283.

87. Magoha, G.A.O., Kaale, R.H. 1995. Epidemiological and clinical aspects of carcinoma of penis at Kenyatta National Hospital. *East African Medical Journal*. 72:359-361.

88. Magoha, G.A.O., Ngumi, Z.W.W. 2000. Cancer of the penis at Kenyatta National Hospital. *East African Medical Journal*. 77:526-530.

89. Chayla, L.P., Rambau, P.F., Masalu, N., Simbila, S. 2015. Ten-year surgical experiences with penile cancer at a tertiary care hospital in northwestern Tanzania: a retrospective study of 236 patients, *World Journal of surgical oncology*. 13:71.

90. Chen, X., Li, X., Garcia, M.M., Gong, K., Song, Y., He, Z., Zhou, L. 2012. Prognostic Factors in Chinese patients with Penile invasive Squamous Cell Carcinoma. *Journal of Andrology*. 33 (6):1276-1281.

91. Koifman, L., Vides, A.J., Koifman, N., Carvalho, J.P., Ornellas, A.A. 2011. Epidemiological aspects of penile cancer in Rio de Janero: Evaluation of 230 cases. International Brazil *Journal of Urology*. 37(2):231-243.

92. Frisch, M., Biggar, R.J., Engels, E.A., Goedert, J.J. 2001. AIDS-Cancer Match Registry Study Group. Association of cancer with AIDS-related immunosuppression in adults. *Journal of the American Medical Association.* 285(13):1736-1745.

93. Joint United Nations Programme on HIV/AIDS (UNAIDS). www.unaids.org/en/regionscountries/countries/southafrica.

94. Novara, G., Galfano, A., De Marco, V., Artibani, W., Ficarra, V. 2007. Prognostic factors in squamous cell carcinoma of the penis. *Nature Clinical Practice Urology.* 4:140-146.

95. Adjiman, S., Zerbib, M., Flam, T. *et al.* 1990. Genitourinary tumors and HIV1 infection. *Journal of European Urology.* 18:61-63.

96. Heyns, C.F., Fisher, M. 2005. The urological management of the patient with acquired immunodeficiency syndrome. *British Journal of Urology International.* 95:709-716.

97. Yuvaraja, T.B., Harshvardhan. 2013. Management of inguinal nodes in carcinoma penis: current concepts. *Amrita Journal of Medicine.* 9(1):1-44.

98. Ornellas, A., Koifman, L., Hampi, D., *et al.* 2013. Radical open inguinal lymphadenectomy for penile carcinoma: surgical technique, early complications and late outcomes. *Journal of Urology.* 190:2086.

99. Ravi, R. 1993. Morbidity following groin dissection for penile carcinoma. *British Journal of Urology.* 72:941.

100. Lopes, A., Hidalgo, G.S., Kowalski, L.P., *et al.* 1996. Prognostic factors in carcinoma of the penis: multivariate analysis of 145 patients treated with amputation and lymphadenectomy. *Journal of Urology.* 156:1637.

101. Gopman, J.M., Djajadiningrat, R.S., Baumgarten, A.S., *et al.* 2015. Predicting postoperative complications of inguinal lymph node dissection for penile cancer in an international multicentre cohort. *British Journal of Urology.* 116:196-201.

102. Jacobellis, U. 2003. Modified radical inguinal lymphadenectomy for carcinoma of the penis: technique and results. *Journal of Urology.* 169(4):1349-1352.

Title of the study: **THE SURGICAL MANAGEMENT OF PENILE CANCER AT THE FREE STATE ACADEMIC COMPLEX: A REVIEW**

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Introduction

Penile cancer is an uncommon malignancy in the Western countries with an incidence of less than 1 per 100 000 men in Europe and the United States. However it is more commonly found in Africa, Asia and South America and accounts for 10% of all cancers in men in certain areas.[1] Some of the known risk factors include uncircumcised status, a history of condylomata accuminata, smoking, and possibly human papillomavirus (HPV) exposure.[2] The vast majority of malignancies of the penis are squamous cell cancers (SCC`s), but other histologic types are observed in 5% of cases. Other histologic subtypes include melanomas, basal cell carcinomas and sarcomas.[4]

The peak incidence of penile cancers is in the sixth and seventh decades of life in Western countries.[5] With Human Immunodeficiency Virus and HPV acting synergistically as promoters of the disease, it is more common to find penile cancer in younger men (3rd to 4th decade of life).[3] There are a few randomized trials exploring treatment options for penile cancer, but due to the small numbers of patients, management is typically based on retrospective reviews from large referral centres.[2]

In South Africa, the treatment of penile cancer is not centralized, patients are treated at different centres throughout the country. To date, there is scarcity of data on surgical management of penile cancer in South Africa.

The aim of this study was:

i.   To describe the profile of men with penile cancer at our centre and compare it to the profile of men as described in the published literature;

ii. To evaluate the incidence of positive lymph nodes and the early complication rate of patients undergoing simultaneous Inguinal lymph node dissection (ILND) during surgery for penile carcinoma; and

iii. To describe the incidence of the different histological subtypes found at the Free State Academic Complex.

Aim/Question

Primary Objective

i. To describe the profile (Age and HIV status) of men with penile cancer in comparison to the published literature.

ii. To evaluate the incidence of positive lymph nodes and the early complication rate of patients undergoing simultaneous ILND during surgery for penile carcinoma.

Secondary Objective

i. To describe the incidence of the different histological subtypes found at the Free State Academic Complex.

Study design

Retrospective descriptive study

Sample

Files of 41 patients diagnosed with penile cancer in the period 2005 to 2015 will be reviewed. Data from the Meditech Computer filling system (Free State Academic Complex Computer filing system) will be used in this review.

Measurement

The data will be collected by the Principle Researcher from the Meditech Computer filing system of Free State Academic Complex after approval by the Ethics Committee of the University of the Free State.

Histology reports of preoperative penile biopsies and definitive penile and lymph node dissection reports will be obtained from the department of Anatomical Pathology NHLS after the consent of NHLS Manager.

The data collected will include demographic date (patient`s age and HIV status) pre-operative penile cancer biopsy results and results of the histology report (histological subtype, tumour stage and grade, site and number of positive inguinal lymph nodes, rate of positive surgical margins and lymphovascular invasion)

The principle researcher will collect the data from the Meditech computer filing system at the Universitas Hospital (part of Free State Academic Complex).

The estimated time for data collection is two weeks and the funds and manpower (Urology Consultants and Registrars) for completion of research will be supplied by the Department of Urology of the University of the Free State.

Information obtained from the files will be transferred to a Microsoft Excel spread sheet.

Analysis of data

Descriptive statistics namely means and standard deviations or medians and percentiles will be calculated for continuous data. Frequencies and percentages will be calculated for categorical data. The analysis will be done by Department of Biostatistics of University of the Free State.

Ethical considerations

Before commencing with the study, the protocol will be submitted to the Ethics Committee of University of the Free State for approval.

I intend to obtain the Consent from the Head of Free State Department of Health after Ethics Committee approval. I also intend to acquire consent from NHLS Pathology for histology results.

REFERENCES

1. Van Poppel, H., Watkin, N.A., *et al.* Penile cancer: 2013. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 00:1-10.

2. Moses, K.A., Winer, A., Sfakianos, J.P., Poon, S.A., Kent, M., Bernstein, M., Russo, P., Dalbagni, G. 2014. Contemporary Management of penile cancer: Greater than 15 year MSKCC Experience. *The Canadian Journal of Urology.* 21(2):7201-70206.

3. Rubin, M.A., Kleter, B., Zhou, M., Ayala, G., Cubilla, A.L., Quint, W.G.V., Pirog, E.C. 2001. Detection and typing of human papilloma virus DNA in penile carcinoma: evidence of multiple pathways of penile carcinogenesis. *The American Journal of Pathology.* 159(4):1211-1218.

4. Cubilla, A.L., Reuter, V., Velazquez, E., Piris, A., Saito, S., Young, R.H. 2001. Histologic classification of penile carcinoma and its relation to outcome in 61 patients with primary resection. *International Journal of Surgical Pathology.* 9:111-120.

5. Chen, X., Li, X., Garcia, M.M., Gong, K., Song, Y., He, Z., Zhou, L. 2012. Prognostic Factors in Chinese patients with Penile invasive Squamous Cell Carcinoma. *Journal of Andrology.* 33 (6):1276-81.