PENILE CANCER

EDITORS

Antonio Carlos L. Pompeo

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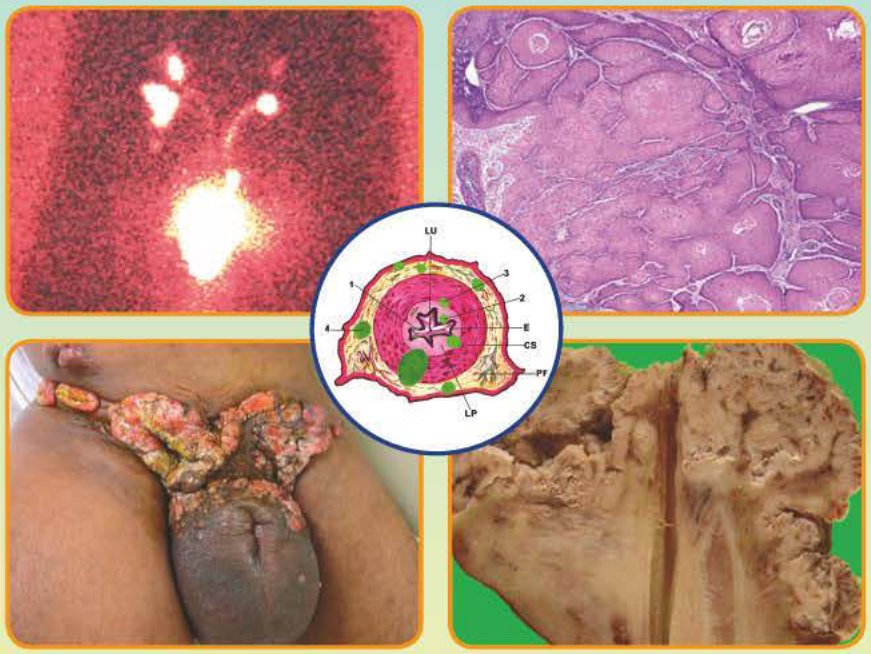
Paul Abrams



INTERNATIONAL CONSULTATION ON PENILE CANCER

Santiago, Chile, November 2008

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PREFACE

In the majority of developed countries, cancer of the penis is an uncommon disease, but it is a significant health and social problem in regions of Africa, Asia, and South America. Squamous cell carcinoma, the most frequent penile cancer, is a malignancy where the behavior is commonly predictable and cure, in initial stages, may be achieved in many instances by partial or total penectomy. On the other hand, more advanced disease comprising regional lymph node or distant metastases has worse and unpredictable outcomes.

There are many controversies regarding the management of all aspects of this cancer, including prevention, staging, treatment options and health policy. The International Consultation on Penile Cancer was designed to present state-of-the-art information on, and understanding of the many aspects of this neoplasia that factor into decisions related to its assessment and therapy. It represents the consensus recommendations of the 8 committees that met in Milan (2008), Santiago (2008) and Chicago (2009) on the occasion of EAU, SIU and AUA meetings. The task of the committee members was to review the literature based on the best evidence, write a text overview of each chapter and finally make recommendations.

On behalf of the ICUD and its steering Committee we want to thank the chairmen and members, composed of representatives of the major urological associations (SIU, AUA, EAU, UAA, CAU) for meeting the highest expectations.

Now it is time to share this textbook with the readers in the hope that the concepts contained will prove useful as information base in approaching their patients and also as stimulation for further studies.

We are very grateful to Drs. Saad Khoury and Paul Abrams of the SIU for having permitted us to organize and edit this book.

Antonio Carlos L. Pompeo, MD, Professor of Urology, ABC Medical School, São Paulo, Brazil, SIU-ICUD Chairman

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Some members of the SIU / ICUD Penile Cancer Consultation, Santiago, Chile, November 2008

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Second row: *Vijay Sangar, Yuvaraja Thyavihally, Vincenzo Ficarra, Hein van Poppel, Susanne Osanto*

Third row: *Antonio Puras-Baez, Antonio Cubilla, Arturo Mendoza-Valdés, Stephen Watya, Andreas Manseck*

Fourth row: *Rowland Rees, Suks Minhas, Alexandre Pompeo, Curtis Pettaway*

Summary of the International Consultation on Urologic Disease Modified Oxford System for Levels of Evidence and Grades of Recommendation*

Levels of Evidence (LE)

Level 1	Metanalysis of randomized controlled trials (RCTs) or a good quality RCT
Level 2	Low quality RCT or metanalysis of good quality prospective cohort studies
Level 3	Good quality retrospective case control studies or case series
Level 4	Expert opinion based on "first principles" or bench research, not on evidence

Grades of Recommendation (GR)

Grade A	Usually consistent level 1 evidence
Grade B	Consistent level 2 or 3 evidence or "majority evidence" from RCTs
Grade C	Level 4 evidence, "majority evidence" from level 2/3 studies, expert opinion
Grade D	No recommendation possible because of inadequate or conflicting evidence

* Adapted from Evidence-Based Medicine. Oxford University. Overview of the main steps for developing and grading guideline recommendations, by P. Abrams, A. Grant, and S. Khoury, January 2004.

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Epidemiology and Natural History of Penile Cancer

M. Pow-Sang

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Epidemiology

Primary malignant penile cancer is a rare disease. Penile cancer incidence varies among different populations, and it is rare in most developed nations. In the United States, age-standardized incidence rates range from 0.3 to 1.8/100,000 inhabitants.[1] Higher incidence rates are seen in underdeveloped countries, such as Uganda (2,8/100,000), and in areas of Brazil (1.5 – 3.7/100,000); the lowest incidence world-wide is reported in Israeli Jews (0.1/100,000).[1]

The overall age-adjusted incidence rate for primary, malignant penile cancer has decreased in the United States,[2], Uganda,[3], Finland[4] and Jamaica.[5]

Penile cancer most commonly affects men between 50 and 70 years of age.[2,6,7] Younger individuals are also affected; approximately 19% of patients are less than 40 years of age[6] and 7% are less than 30 years.[6,8] In a study by Hernandez et al. evaluating the socioeconomic status of patients with penile squamous cell carcinoma, they found that the risk was 43% higher among men from countries with 20% or more of the population at the poverty level compared with men living in regions of less than 10% poverty.[9] There is an increase in incidence of regional disease in recent years (1993-2002) when compared to 1973-1982 and 1983-1992.[2] Familial association of penile cancer has been reported in Sweden, with a high standardized incidence rate in the offspring of fathers with penile cancer (standardized incidence ratio (SIR) = 6.86; 95% confidence interval (CI) = 1.78 – 17.73). The cancer risk for offspring according to concordant cancer in any familial proband (sibling, mother or father) is 7.54 for penile squamous cell carcinoma (SCC).[10]

- Incidence rate for primary malignant penile cancer has decreased in the United States, Uganda, Finland and Jamaica (LE 4).
- Penile cancer affects men between 50 and 70 years of age (LE 4).
- There is an increase in incidence of regional disease in recent years (LE 4).
- There is familial association of penile cancer (LE 4).

Risk factors

Case-control studies have shown the association of risk factors for invasive penile carcinoma. Factors positively associated with CIS or invasive cancers are the presence of phimosis, injury to the penis, cigarette smoking, genital warts and human papillomavirus (HPV) infection (Table 1).

Table 1: Risk factors for invasive penile carcinoma

- Presence of phimosis
- Injury to the penis
- Chronic balanitis
- Ultraviolet radiation
- Cigarette smoking
- Genital warts
- HPV infection

▪ Phimosis

The most important etiologic factor for invasive penile cancer is the presence of an intact foreskin. It is rarely seen in Jews who are circumcised at birth.[11] Many studies suggest that circumcision protects against invasive penile cancer by preventing phimosis. Most observational studies also suggest that male newborn circumcision is

associated with a decreased risk of penile cancer. A history of phimosis is found in approximately 25% of penile cancer patients. Another study in Brazil has shown the presence of phimosis in 60% of patients with penile cancer.[6] In a study by Madsen et al.[12] phimosis (odds ratio (OR) = 3.39; 95% CI = 1.62 – 7.11) was significantly associated with risk of penile SCC. Tseng et al.[13] analyzed the data from 100 matched case-control pairs. In this study, cases of carcinoma in situ (CIS) and invasive penile cancer were analyzed separately as well as together. Phimosis was strongly associated with invasive carcinoma (adjusted OR = 16, 95% CI = 4.5 – 57) but not CIS (OR = 1.7, 95% CI = 0.32 – 7.8), and these associations persisted when the analyses were restricted to uncircumcised subjects. Furthermore, circumcision during infancy was inversely associated with invasive carcinoma (OR = 0.41, 95% CI = 0.13 – 1.1). Hellberg et al.[14] carried out a retrospective study of 244 men with penile cancer and 232 matched controls. The relative risk of having penile cancer among men with phimosis was 64.6 (95% CI = 30 – 135). Maden et al.[15] reported a study of 110 men with penile cancer and 355 control subjects. This study found a 3.5-fold elevated risk (95% CI = 1.7 – 7.4) associated with difficulty in retracting the foreskin, controlling for age and skin laceration. The risk of penile cancer was 3.2 times greater among men who had never been circumcised relative to men circumcised at birth and 3.0 times greater among men who had been circumcised after the neonatal period. Brinton et al.[16] found an increased penile cancer risk associated with later circumcision; they reported a relative risk for penile cancer of 38 and 11 for uncircumcised men with phimosis and paraphimosis, respectively. In this study, circumcision was performed largely for redundant prepuce or phimosis, and was associated with an approximately 30-fold excess risk of penile cancer. In a case-control study by Daling et al.[17] phimosis was more common in cases (35.2%) than controls (7.6%) among those men who were not circumcised in childhood (OR = 7.4; 95% CI = 3.7 – 15). Men who were never circumcised or were circumcised later in life were more likely to have tumors located on the glans than men who were circumcised in childhood.

- The presence of phimosis is a risk factor for developing penile cancer (LE 3a).
- Circumcised males are less prone to develop penile cancer (LE 3a-4).

▪ Circumcision

Schoen et al.[18] evaluated the relation between newborn circumcision and invasive penile cancer among adult male members of a large health maintenance organization. Of 89 men with invasive penile cancer whose circumcision status was known, 2 (2.3%) had been circumcised as newborns, and 87 were not circumcised. The relative risk of invasive penile cancer for uncircumcised to circumcised men was 22:1.

The protective effect of circumcision is likely due to the lack of accumulation of smegma, which forms from desquamated epithelial cells. Retention of smegma has been experimentally demonstrated to be carcinogenic in mice.[19] To date, the precise carcinogenic substance in smegma is not known. The collection of smegma may lead to inflammation and chronic irritation of the genital area. This process might be aggravated by lack of personal hygiene. Other mechanisms may explain the protective effect of circumcision in sexually transmitted diseases. The penile shaft and the outer surface of the foreskin of circumcised men are covered by a keratinized stratified squamous epithelium that provides a protective barrier against HPV infection.[19] Thicker and more keratinized skin may confer some resistance to HPV entry.[20] The glans/corona of an uncircumcised man is normally covered by the unretracted foreskin. During sexual intercourse, the foreskin becomes retracted, exposing both the glans/corona and inner foreskin. The inner mucosal surface of the foreskin is not keratinized and may be a weaker barrier for infection and may be more vulnerable to the virus.[21] It has been suggested that retraction of the foreskin during intercourse exposes the inner mucosal surface to HPV and that access to basal cells is further facilitated through tears and abrasions, which can occur during intercourse.[22-24]

- Newborn circumcision may confer a protective effect against invasive penile cancer (LE 4).

▪ Cigarette smoking

Another factor associated with invasive carcinoma of the penis or CIS or both is cigarette smoking. Winkelstein[25] hypothesized that smoking influences squamo-epithelial carcinogenesis, not only in parts of the body in direct contact with inhaled smoke but also at distant sites via the circulatory system. Another hypothesis mentions that constituents of cigarette smoke act in the presence of bacteria associated with chronic irritation and infection to promote malignant transformation.[26] A tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) was found in the urine of smokers.[27] NNK metabolism takes place in a few tissues and it is eventually excreted largely in the urine and to a smaller extent in saliva, faeces and secretions from preputial glands.[28] Accumulation of carcinogens in smegma may be an important factor. Harish and Ravi[29] evaluated 503 patients with squamous cell carcinoma of the penis and 503 age-matched controls. They found that tobacco in the form of cigarettes was a risk factor for penile carcinoma (OR = 1.44; 95% CI = 1.11 - 1.85). A significant amount of risk was seen for those who smoked >10 cigarettes a day (OR = 2.14; 95% CI = 1.43 – 3.21) and those who had smoked for >5 years (OR = 1.43; 95% CI = 1.10 – 1.83). A significant association was noted with a lifetime exposure to >30 pack years (OR = 1.86; 95% CI = 1.21 - 2.87). In this study, chewing tobacco was a significant risk factor for penile carcinoma, with 34% of patients in the habit of chewing tobacco as against 15.5% of controls (OR = 3.11; 95% CI = 2.21 – 4.37). A total of 59.4% of patients either smoked or chewed tobacco and 12.3% of patients used both. Either habit was a risk factor (OR = 2.29; 95% CI = 1.73 – 3.30), and a combination of both habits carried a higher risk (OR = 3.39; 95% CI = 2.08 – 5.53). Tseng et al.[13] found that the incidence of penile cancer (CIS and invasive combined) among men who had ever smoked cigarettes was 2.4 times that of men who had never smoked (95% CI = 0.86 – 7.3). The rate was higher among current smokers (OR = 3.1; 95% CI = 0.93 – 11) than among ex-smokers (OR = 1.6; 95% CI = 0.44 – 6.9), and it was appreciably higher for men who currently smoked more than 20 cigarettes per day (OR = 5.9; 95% CI = 1.4 – 24) than among men who smoked fewer than 20 cigarettes per day (OR = 1.2; 95% CI = 0.33 – 4.1). Hellberg et al.[14] found that smoking had a significant effect on the prevalence of penile cancer even when the amount of smoking was not considered. There was a clear dose-response relation, with smokers of more than 10 cigarettes a day having a significantly higher risk than light smokers (one to ten cigarettes a day) (relative risk (RR) = 2.22; 95% CI = 1.34 – 3.69). Maden et al.[15] also found that the risk of penile cancer among men who smoked at diagnosis was 2.8 times that of men who never smoked (95% CI = 1.4 – 5.5). In this study, among men who smoked at diagnosis, lifetime smoking of more than 45 pack-years of cigarettes elevated the risk to 3.2 times that of men who never smoked (95% CI = 1.4 – 7.2). An epidemiologic study by Favorito et al.[6] reported tobacco smoking in 101 of 283 patients (35.68%) with penile cancer. Madsen et al.[12] found that cumulative tobacco consumption was dose-dependently associated with risk of penile SCC ($P_{trend} = 0.009$).

- Tobacco smoking is a risk factor for penile cancer (LE 3a-4).
- Chewing tobacco is a risk factor for penile cancer (LE 3a).

▪ Injury to the penis and chronic balanitis

Injury to the penis is another risk factor associated with penile cancer. The adjusted OR for history of an injury to the penis that occurred more than 2 years before diagnosis was 23 (95% CI = 4.4 – 124) for CIS and 4.6 (95% CI = 0.44 – 43) for invasive penile cancer.[13] Maden et al. also found, after adjustment for a history of penile rashes and genital warts, that a history of small tears or abrasions of the penis was associated with a risk of 3.9 (95% CI = 1.9 – 7.7) relative to men without such a history.[15] Daling et al. reported an increased risk of penile cancer in men with penile tear (OR = 5.2, 95% CI = 3.1 – 8.7), and penile injury (OR = 3.2, 95% CI = 1.5 – 6.8).[17]

Hellberg et al.[14] found that a history of one or more episodes of balanitis was significantly more common among men with penile cancer, with a RR 9.49 (95% CI = 5.2 – 17.2). In a study by Madsen et al.[12], balanitis (OR = 3.07; 95% CI = 1.36 – 6.93) was significantly associated with risk of penile SCC.

- Injury to the penis is a risk factor for penile cancer (LE 3a).
- Balanitis is a risk factor for penile cancer (LE 3a).

▪ Genital warts

A history of warts on or around the genital or rectal area that occurred 2 or more years before the reference date increased the rates of both CIS (OR – 1.7; 95% CI = 0.41 – 7.2) and invasive penile carcinoma (OR = 3.7; 95% CI = 0.81 – 15).[13] Maden et al. reported that the risk of penile cancer in men with a history of genital warts was 5.9 times that of men with no such history (95% CI = 2.1 – 17.6).[15] In a case-control study by Daling et al.[17], of men with penile cancer 25.7% reported a history of genital warts compared to 4.8% of controls (OR = 7.6, 95% CI = 4.3 – 13.5).

- Genital warts are more common in patients that have penile cancer (LE 3a).

▪ HPV Infection

Many studies suggest an association between human papillomavirus (HPV) infection and penile cancer. The mechanism by which HPV leads to malignant transformation is likely mediated through two viral genes, E6 and E7, which are actively transcribed in HPV infected cells. The most recognized target of HPV E6 protein is TP53,[30] whereas the primary target of HPV E7 protein is RB1 and the related pocket proteins, p107 and p130.[31] The E6 and E7 proteins bind to and inactivate the host cell's tumor suppressor gene products p53 and pRb (retinoblastoma gene) both of which are known negative regulators of cellular proliferation, leading to uncontrolled growth.[32] In cervical carcinogenesis, recombination between HPV and chromosomal DNA is frequent and likely necessary for progression, and DNA hypermethylation – specifically of the L1 gene - is a biomarker for cancerous progression.[33] Recently, Kalantari et al.[34] compared penile and cervical carcinoma with HPV 16 and HPV 18. They found numerous striking similarities: high HPV 16 methylation rates in penile carcinomas resemble those reported in cervical malignant lesions. They proposed that both penile and cervical carcinomas depend on recombination as a necessary step in the etiological process. Their data support the causality of HPV infection in the etiology of penile cancer and suggest similar etiological and epidemiological parameters for HPV dependent cervical and penile carcinogenesis.

In a systematic review of the literature, Dunne et al.[35] found a wide range (1% to 73%) of genitourinary HPV prevalence among men worldwide, 15 (56%) of these studies reported a prevalence of >20%, which is similar to the HPV prevalence found among women (27%).[36] Many studies have evaluated the distribution of HPV in men (Table 2).

Table 2: Distribution of HPV in men

	Foreskin	Prepuce internal surface	Prepuce external surface	Penile shaft	Scrotum	Glans	Urine	Urethra	Semen
Weaver et al.[37]	28%	-	-	24%	17%	16%	6%	-	-
Giuliano et al.[38]	-	-	-	49.9%	34.2%	35.8%	-	10%	5.3%
Nielson et al.[39]	-	-	-	40.5%	25.1%	32.5%	-	11.3%	5.6%
Hernandez et al.[40]	-	-	-	52%	40%	32%	10%	-	6%
Nicolau et al.[41]	-	44%	24%	-	12%	24%	-	30%	-

It has been shown that there is a lower prevalence of penile HPV in men who have been circumcised.[22,41,42] There is an association between the mean number of female sexual partners in the year preceding the study and the presence of HPV DNA. The higher the number of sexual partners, the greater the chance of acquiring and transmitting HPV.[12,22,43,44]

Penile cancer, like cervical cancer, is caused by high-risk HPV, but penile cancer is 10 times less common than cervical cancer;[45] The overall prevalence of HPV-DNA in penile cancer ranges between 15% and 81% (Table 2). Many case-control studies have shown the presence of HPV types 16 and 18 in penile carcinoma. HR-HPV has been detected in 24% to 65% of penile cancer cases, compared to 12% of controls.[12,17,46,47] Specifically, penile carcinoma is associated with HPV 16 in 25% to 94.7% and HPV 18 in 10.5% to 55.4% of the cases (Tables 3 and 4).

Table 3: Overall prevalence of HPV DNA in penile carcinomas

Reference	n	HPV-positive (%)
McCance et al.[51]	53	51
Iwasawa et al.[52]	111	63
Maden et al.[15]	67	49
Chan et al.[53]	41	15
Cupp et al.[54]	42	55
Gregoire et al.[55]	117	22
Picconi et al.[56]	38	71
Rubin et al.[49]	142	42
Guerrero et al.[57]	10	40
Tornesello et al.[58]	41	46
Scheiner et al.[59]	80	72
Bezerra et al.[60]	82	30
Pascual et al.[61]	49	77
Giuliano et al.[38]	303	65
Nielson et al.[39]	463	65
Rombaldi et al.[44]	99	54
Ding et al.[62]	28	61
Suzuki et al.[63]	13	54
Senba et al.[64]	65	81
Salazar et al.[65]	54	65

Table 4: Prevalence of HR-HPV in penile carcinomas

	HPV 16 (%)	HPV 18 (%)
Guerrero et al.[57]	25	75
Varma et al.[66]	65	-
Bezerra et al.[60]	52	-
Maden et al.[15]	63	-
Rubin et al.[49]	60	-
Pascual et al.[61]	84.2	10.5
Lont et al.[67]	76	-
Scheiner et al.[59]	52	-
Tornesello et al.[59]	94.7	-
Senba et al.[64]	-	55.4

In men, productive HPV infection can result in simple condyloma acuminatum, giant condyloma, or Buschke-Löwenstein tumor, mainly caused by HPV 6 and 11. HPV-associated penile intraepithelial neoplasias (PIN) are found in the great majority of cases, but they are inconspicuous lesions caused by high-risk HPV types, especially HPV 16 and 18, histologically showing low, moderate, or severe dysplasia (PIN grades 1, 2 and 3).[48]

Rubin et al. evaluated the prevalence of HPV DNA in different histological subtypes of penile carcinoma, dysplasia, and condyloma.[49] HPV DNA was detected in 42% cases of penile carcinoma, 90% cases of dysplasia, and 100% cases of condyloma. In this study, although keratininzing SCC and verrucous carcinoma were positive for HPV DNA in only 34.9% and 33.3% of cases, respectively, HPV DNA was detected in 80% of basaloid and 100% of warty tumor subtypes.[49] Cubilla et al.[50] reported detection of HPV 16 in 9 of 11 (81%) cases of basaloid and 3 of 5 (60%) cases of warty SCC of the penis.

- High risk HPV is frequently found in penile cancer patients (LE 3a-4).

NATURAL HISTORY

At presentation, SCC is found on the glans in 48% of cases, the prepuce in 21%, glans and prepuce in 9%, coronal sulcus in 6%, and shaft in <2%.[68] It is usual for many of these patients to delay seeking medical attention, and it has been reported that 25% to 50% of patients have the penile lesion for more than a year prior to diagnosis.[69-71]

The clinical presentation of penile SCC is variable, and can range from an area of subtle induration to a small excrescence, papule, exophytic or flat and ulcerative lesion. Itching or burning under the foreskin, as well as the presence of ulceration of the glans or prepuce, are the most commonly reported symptoms; pain is usually not a presenting complaint.[72,73]

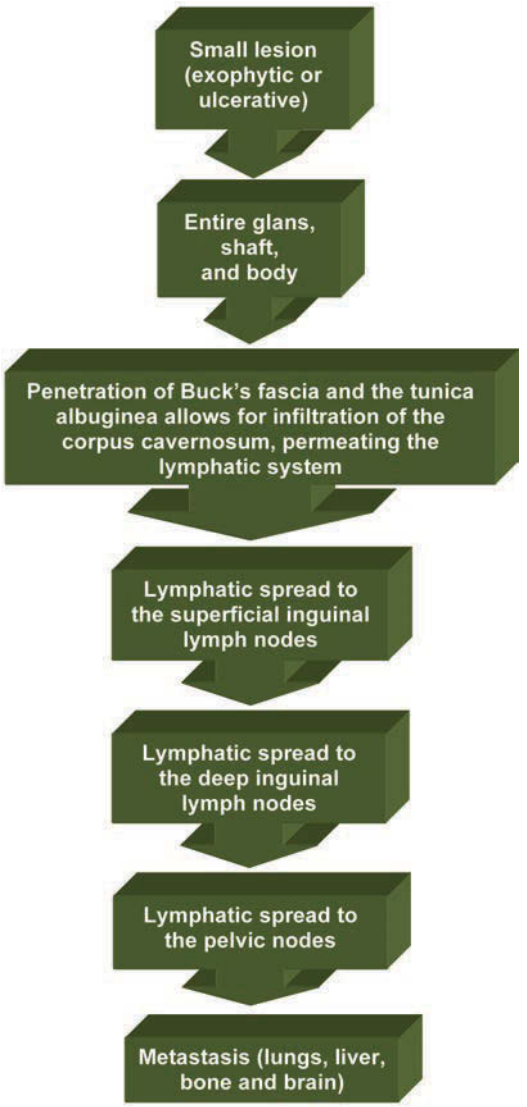

Fig. 1: *Natural history of penile cancer.*

Fig. 2: *Penile tumor originating on the glans.*

Lesions usually originate on the glans (Fig. 2) and gradually extend to involve the entire glans and shaft of the penis. Phimosis may obscure a lesion and allow a tumor to progress silently. Eventually, erosion through the prepuce, foul preputial odor and discharge with or without bleeding call attention to the disease (Fig. 3). Buck's fascia acts as a temporary natural barrier to local extension of the tumor, protecting the corporal bodies from invasion. Penetration of Buck's fascia and the tunica albuginea permits penetration of the corpus cavernosum and may permeate the lymphatic system.

The lymphatics of the penis form richly anastomosing channels that cross the midline along the shaft and at the penile base. Therefore, cross-inguinal lymph node metastasis may occur. Penile autoamputation may occur as a late result (Fig. 4). As with SCC of other areas of the body, penile SCC has a particular tendency for lymphatic spread to the superficial and deep inguinal lymph nodes and, subsequently, to the pelvic nodes (Fig. 5-6). Penile lymphangiogram studies demonstrate consistent patterns of drainage that proceed from superficial inguinal to deep inguinal to pelvic node sites without evidence of "skip" drainage.[74] If untreated, the inguinal metastases enlarge, ulcerate through the skin (causing infection) (Fig. 7) or grow into the adjacent femoral vessels producing exsanguinating hemorrhage.[75]

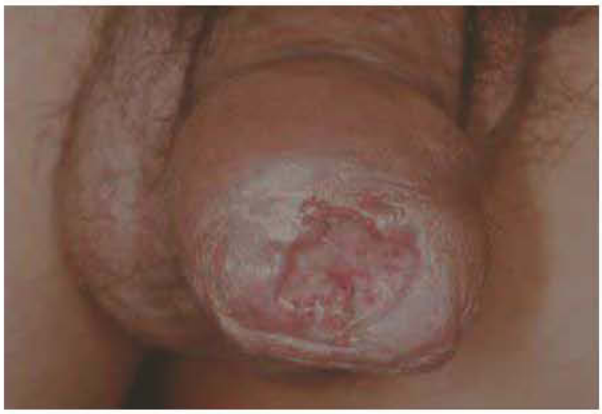

Fig. 3: *Patient with phimosis and an exophytic lesion on the glans penis.*

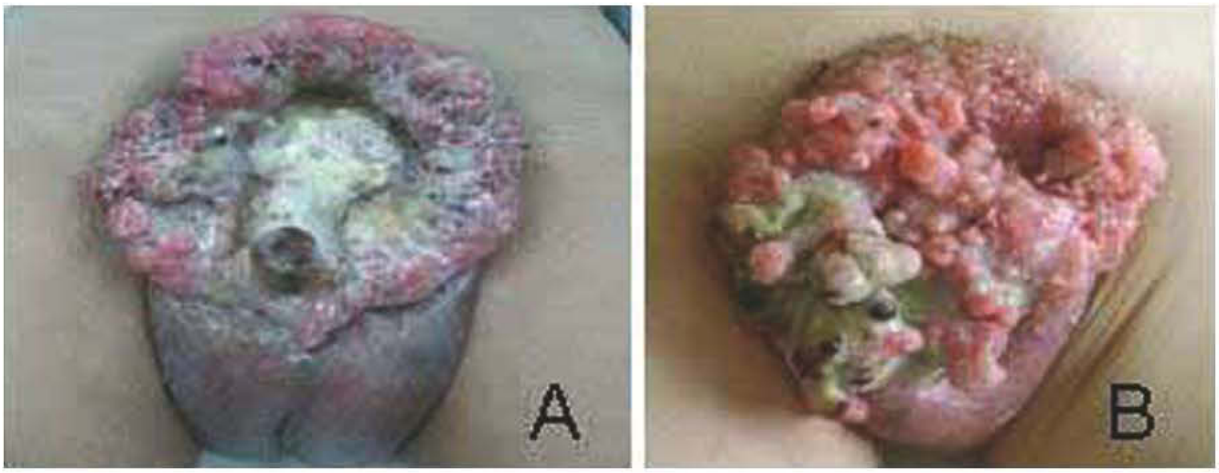

Fig. 4: *Autoamputation of the penis due to infiltrative penile cancer.*

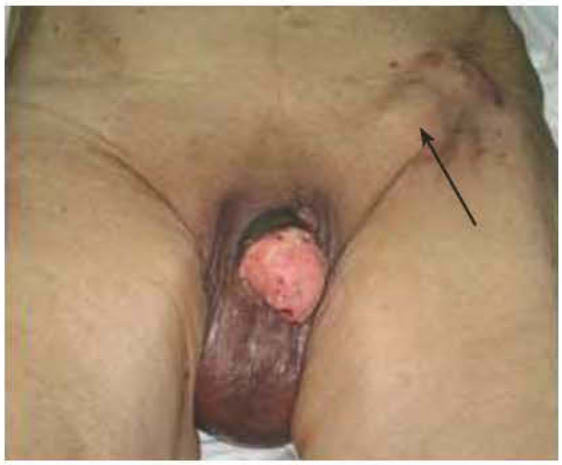

Fig. 5: *Patient with a lesion on the glans penis and lymphatic spread to the superficial inguinal lymph nodes (black arrow).*

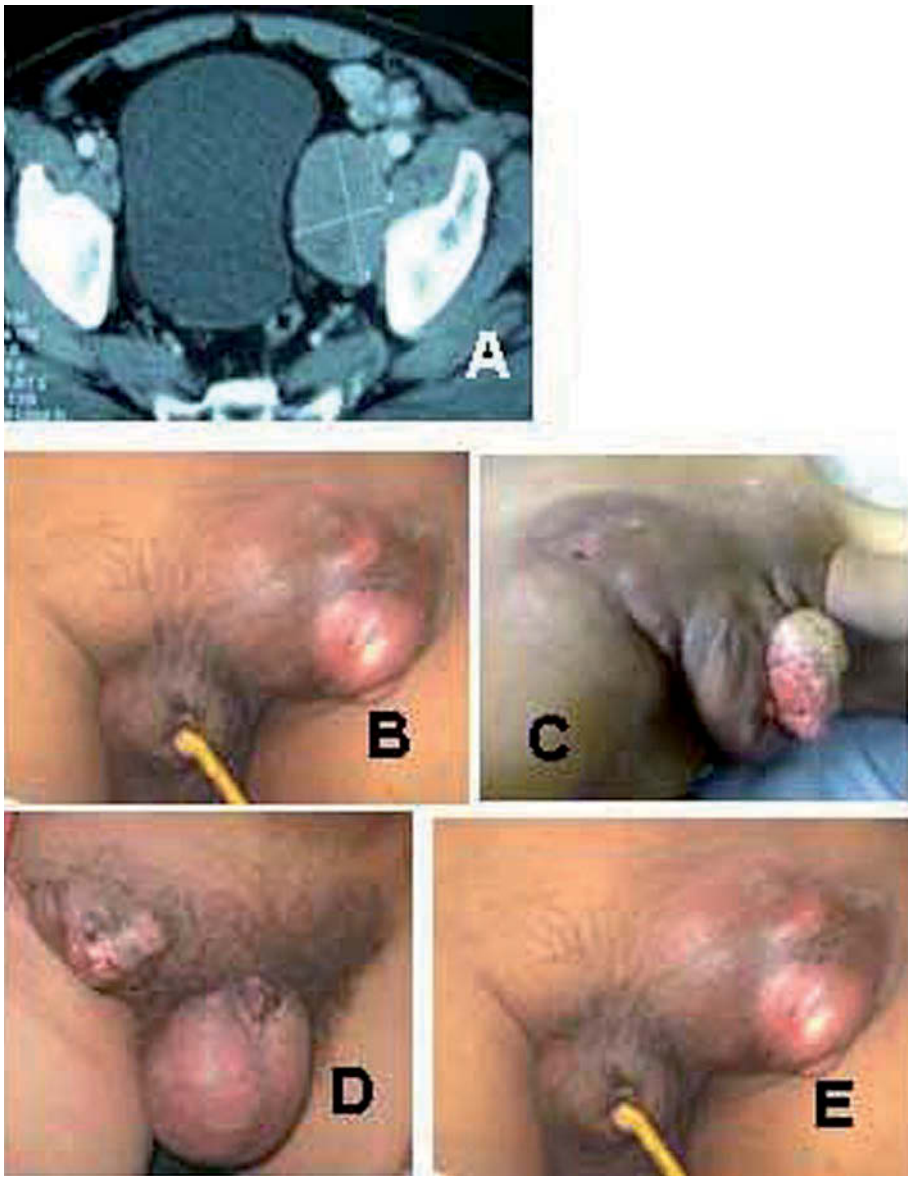

Fig. 6A: *Patient with penile cancer and lymphatic spread to the pelvic nodes.*

Fig. 6B, C, D, E: *Penile cancer and lymphatic spread to the inguinal nodes.*

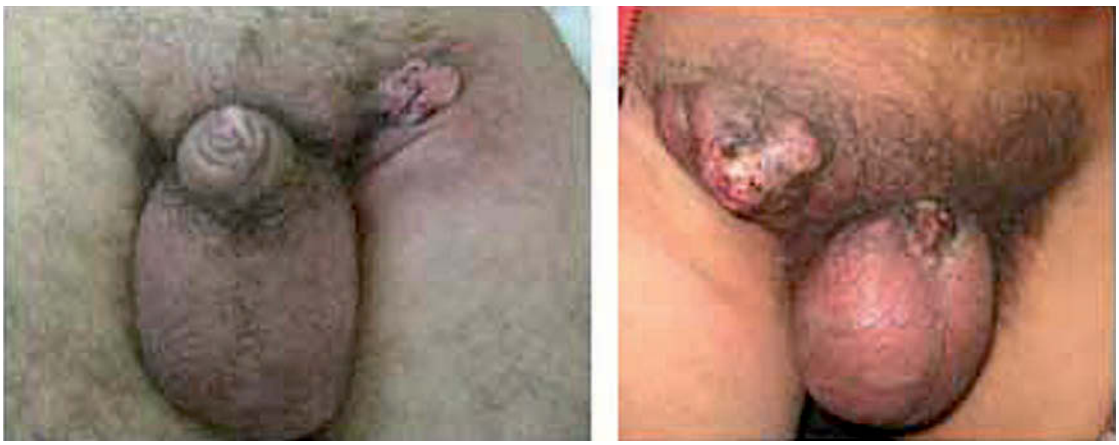

Fig. 7: *Ulceration of inguinal metastasis from penile cancer.*

Without treatment, patients with penile SCC usually die within 2 years after diagnosis of the primary lesion, because of complications due to uncontrollable locoregional growth or from distant metastases.[72,73] Metastatic spread to distant sites (lungs, liver, bone and brain) (Fig. 8) is uncommon and is reported to occur in 1% to 10% of cases in most large series. Such metastases usually occur late in the course of the disease after the local lesion has been treated.[8] Distant metastases in the absence of regional node metastases are unusual.

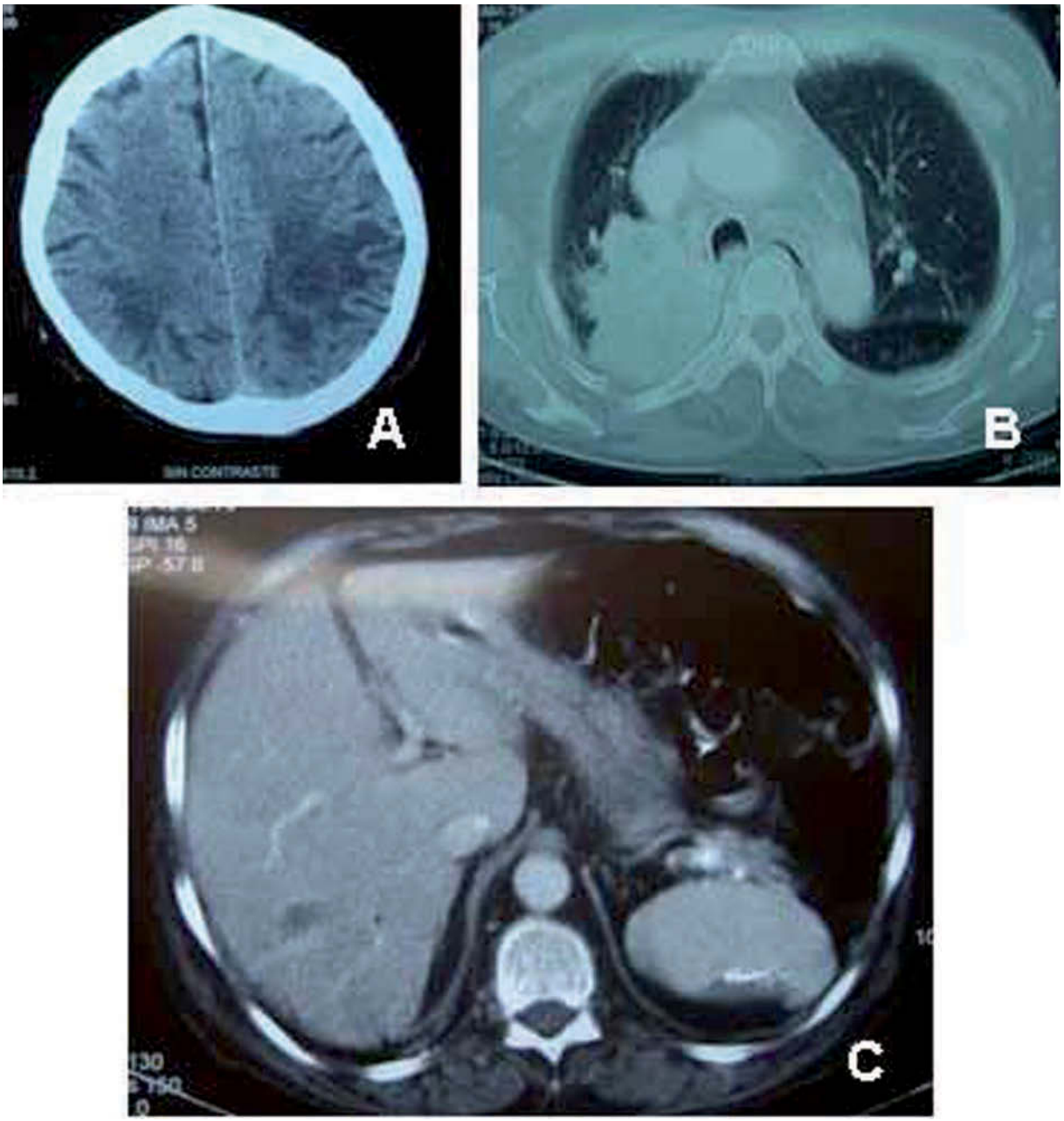

Fig. 8: *Metastatic spread from penile cancer to the brain (A), lung (B) and liver (C).*

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Committee 2

Developments in the Pathology of Penile Cancer

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Developments in the Pathology of Penile Cancer

Developments in the Pathology of Penile Cancer

A. L. Cubilla

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Anatomical features

An understanding of the anatomy of the penis is important because many diagnostic and prognostic concepts of penile tumors are based on anatomical considerations.[1-4] The penis is composed of three portions: the distal part (glans or head), mid part (corpus or shaft), and proximal part (root). This description focuses on the distal portion, which is the site of most epithelial tumors. The penile anatomical layers are depicted in Fig. 1.

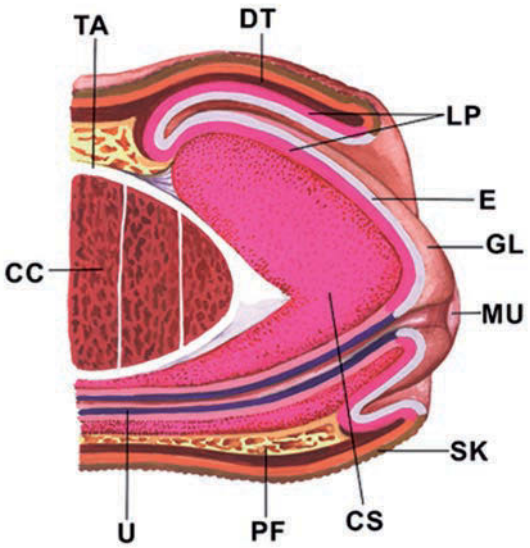

Fig. 1: **Penile anatomical layers:** *The most distal portion of the penis is the glans (GL) covered by a non-keratinized stratified squamous epithelium (E) resting over a band of connective tissue or lamina propria (LP). The erectile tissue of the corpus spongiosum (CS) expands distally to form most of the glans; the penile urethra (U) is ventral as well as the meatus urethralis (MU). Deeper lie the corpora cavernosa (CC), forming most of the penile shaft, and separated from the corpus spongiosum by the tunica albuginea (TA), a dense band of connective tissue. The penile (Buck's) fascia (PF) is a loose connective tissue located between the tunica albuginea and the skin of the shaft and extends up to the coronal sulcus. The foreskin has an inner (mucosal) surface similar to the glans with the same type of epithelium and lamina propria, and an outer (cutaneous) surface, similar to the skin of the shaft (SK); between the lamina propria and the skin lies the muscular layer, dartos (DT).*

Gross features

The glans and coronal sulcus are encased by the foreskin, the inner surface of which is lined by a smooth mucosa common to penile distal epithelial compartments, glans, sulcus, and foreskin. The meatus urethralis is vertical and from it the frenulum arises to its insertion at the glans. The corona is a circumferential rim at the base of the glans. The glans cut surface reveals four anatomical layers: epithelium, lamina propria, corpus spongiosum, and corpora cavernosa. The corpora are separated by the tunica albuginea; the distance between the lamina propria and the tunica albuginea is variable (Fig. 2). The penile (distal) urethra is ventrally located and is surrounded by the erectile tissue of the corpus spongiosum. It shows epithelial alterations in association with penile cancer[5] and it is a common site of positive resection margin in partial penectomy.[6] Also, primary urethral tumors may be confused with penile neoplasms.[7] The foreskin covers the external surface of the penis and distally reflects over the preputial orifice. The external (skin) surface is dark and wrinkled and the inner mucosal surface is pale and smooth.[8] Most preputial carcinomas arise on the mucosal surface of the foreskin.

Preputial length is variable and this variation is important in the pathogenesis of penile cancer, which is more common in long foreskins, which entirely cover the glans. In intermediate length foreskins the preputial orifice is located between the meatus and corona and in the short variant the preputial orifice is located proximally to the corona (Fig. 3).[9] The coronal sulcus (also named balano-preputial sulcus) is a *cul-de-sac* located between the glans corona and foreskin.

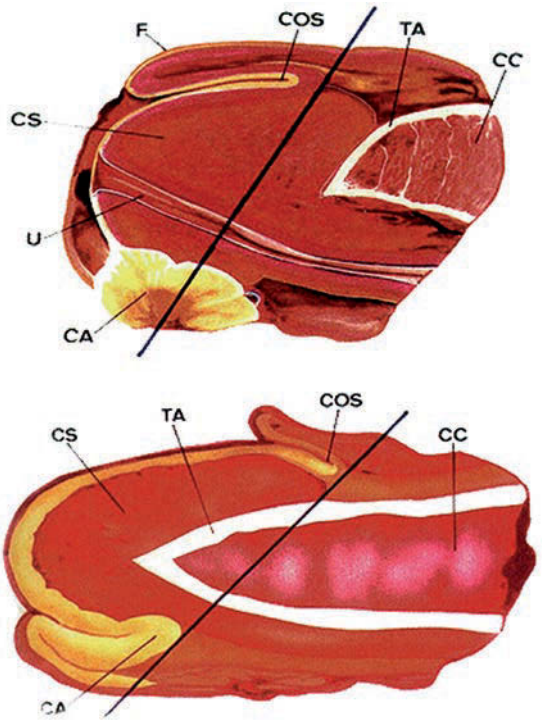

Fig. 2: **Anatomical variability:** *A line passing through the coronal sulcus (COS) separates the glans from the shaft. The CC is not part of the glans in a third and inserts within the glans in two-thirds of the cases. CS: corpus spongiosum; CC: corpus cavernosum; U: penile urethra; F: foreskin; CA: penile carcinoma.*

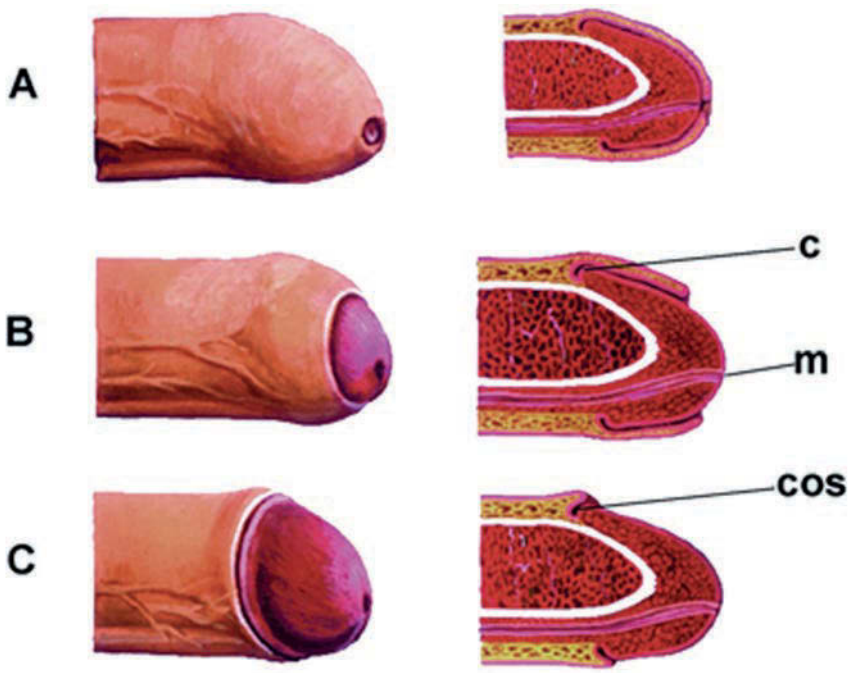

Fig. 3: **Types of foreskin:** *In the long type (top) the foreskin entirely covers the glans and the preputial orifice. In the intermediate-type (middle) the preputial orifice is between the meatus and the glans corona. In the short-type variant (bottom) the preputial orifice is between the glans corona and the coronal sulcus.*

Microscopic features

The glans of uncircumcised men is lined by a layer of six to ten cells thick forming a non-keratinizing epithelium. The lamina propria measures 2 to 3 mm thick and is composed of loose connective tissue containing small blood and lymphatic vessels and nerves. The corpus spongiosum consists predominantly of complex and inter-anastomosed venous sinuses (the erectile tissue) separated by fibrous trabeculae. The thickness of the corpus spongiosum varies from 6 to 13 mm.[10] The corpora cavernosa, the main component of the shaft, are part of the glans in more than two-thirds of specimens (Fig. 2).[10] The corpora cavernosa are predominantly composed of thick and inter-anastomosing erectile vascular structures separated by a complex network of trabeculae. The vessel walls are composed of thick bundles of smooth muscle. The vascular structures of the corpora cavernosa are thicker and more complex when compared with those of the corpus spongiosum. The interstitial connective tissue contains more smooth muscle bundles than in the corpus spongiosum.[4] The tunica albuginea is a 1-3 mm thick hyaline fibrous sheath separating corpus spongiosum and corpora cavernosa. Small nutritional vessels and adipose tissue traverse the tunica from the penile fascia to the erectile tissues, explaining pathways of occasional tumor invasion to the corpus cavernosum from Buck's fascia. Buck's fascia entirely encases the shaft and extends to the coronal sulcus. Its highly vascular and loose connective tissue favors tumor extension from the glans and coronal sulcus to the shaft and resection margins.[7]

The foreskin shows five histological layers: squamous epithelium, lamina propria, dartos, dermis and epidermis. The inner epithelium is non-keratinizing squamous, similar to that of the glans. The lamina propria is thin and composed of loose fibrous tissue containing small vessels and nerves. The dartos is wider and is made of loose connective tissue associated with numerous irregularly arranged bundles of smooth muscle, vascular structures, nerves and pacinian corpuscles. The skin is wrinkled and pigmented. Numerous genital Meissner neural corpuscles are present. No skin adnexa are present, except for scarce and small sebaceous glands not associated with hair follicles.[4] Mucinous metaplastic cells have been reported in association with chronic inflammation.[11] The coronal sulcus rarely is the site of a primary penile tumor. Its anatomical levels have been recently studied and are variable: epithelium, lamina propria, dartos and Buck's fascia or epithelium, lamina propria and Buck's fascia.[4]

Squamous cell carcinoma

▪ General features

The majority of penile cancers are squamous cell carcinomas (SCC) but there is a variegated spectrum of histological subtypes. They originate in the mucosal surface of the penis extending from the preputial orifice to the urethral meatus.[12] Glans tumors predominate over those exclusive of the foreskin or sulcus.[13-15] SCCs of the outer skin of the foreskin or the shaft are exceedingly uncommon. Carcinomas of the distal urethra are also rare and show features similar to some glans penile cancers. Although they are not strictly urothelial (the distal urethral epithelium is not urothelial) and share morphological features with penile cancers, they are usually not discussed with penile but with urothelial neoplasms.[6]

The mean age of patients with penile SCC is about 60 years. Human papillomavirus (HPV)-related tumors such as warty and basaloid cancers affect younger patients (45-55 years) and verrucous and pseudohyperplastic carcinomas occur at an older age (70-80 years).[16] An exophytic mass or ulcerated lesion is the usual presenting sign. In non-western countries, up to 40% of patients present with inguinal lymph node metastases and 10% with disseminated disease. This high figure contrasts with a significantly lower incidence of regional and systemic metastases in North American patients (13% and 2.3% respectively).[17] The frequency of *in situ* and invasive carcinomas varies according to geographical regions. In areas of high frequency, the majority of tumors are initially diagnosed as invasive tumors whereas in regions of low incidence, most cases are diagnosed as *in situ* lesions (4% and 33% in Paraguay and USA, respectively). Geographical differences may reflect the incidence of invasive cancers. If all precancerous and invasive lesions are taken into account the difference would diminish or vanish.

About half of penile carcinomas are SCCs of the usual type and the other half are distinctive morphological variants with different prognosis. The WHO classification, published in 2004 is outdated. An extended modified classification is to be published in the upcoming AFIP fascicle (Epstein J, Humphrey P, Cubilla AL. Tumors of the Prostate Gland, Seminal Vesicles, Male Urethra and Penis. Washington, DC: Armed Forces Institute of Pathology; 2010 [forthcoming]).

▪ Squamous cell carcinoma, usual type

SCC of the usual type accounts for about 50%-60% of all penile carcinomas.[18] Grossly, there are irregular white gray exophytic to flat and reddish ulcerated endophytic masses. The cut surface shows white gray neoplastic tissues invading penile anatomical planes. Microscopically, tumors vary from well differentiated keratinizing to solid anaplastic carcinomas with scant keratinization (Figs. 4 and 5). Detailed criteria for grading penile carcinoma were recently published.[19] Most tumors are highly keratinized and of moderate differentiation. Poorly differentiated carcinomas may have variable amounts of spindle cell, giant cell, solid, acantholytic, clear cell, small cell, warty, basaloid or glandular components. When these features predominate, there is a morphological justification for separation of the neoplasms as special subtypes of SCCs.

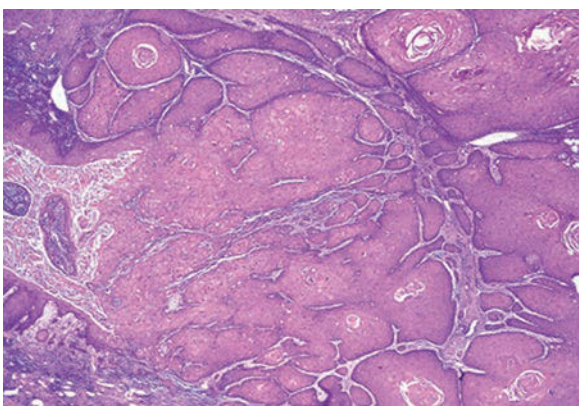

Fig. 4: *Well differentiated (grade 1) usual SCC. Irregular nests composed of neoplastic cells with minimal nuclear atypia and gradual keratinization; cells are almost undistinguishable from normal epithelium.*

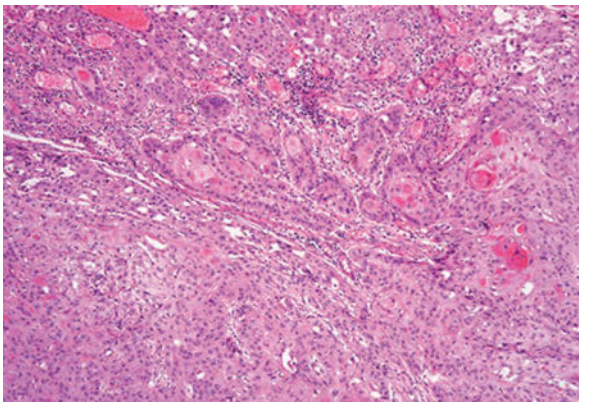

Fig. 5: *Moderately-to-poorly differentiated (grades 2-3) usual SCC. Nuclear atypias are more evident in grade 2, but keratinization is still present (lower and upper right fields); in grade 3 (upper left field) anaplastic cells, with nuclear pleomorphism, prominent nucleoli, irregular nuclear membrane, coarse chromatin and abundant and atypical mitosis, are identifiable.*

▪ Verrucous carcinoma

Verrucous carcinomas are slow-growing, extremely well differentiated tumors, with a papillomatous appearance and broadly based limits between tumor and stroma. Described by Dr Lauren Ackerman in 1948 in the oral mucosa[20] it continues to pose diagnostic problems with other verruciform tumors; condylomas, papillary and warty carcinomas have been published under the designation of verrucous carcinomas or Buschke-Löwenstein tumor, and considerable confusion exists in the literature regarding the proper designation of this neoplasia.[21] A proposed classification for verruciform neoplasms clarifies the differential diagnosis (Fig. 6).[22] If they are correctly diagnosed verrucous carcinomas show no metastases.[23,24] The tumor can be locally aggressive but it is biologically benign and should be treated according to this.[25,26] Verrucous carcinoma may be associated with sarcomatoid carcinoma sporadically or after radiation therapy.[27] HPV infection has been consistently reported as rare or negative.[28] They are unusual neoplasms accounting for 7% of all penile SCCs. Verrucous carcinomas occur during the 6 to 7th decades.

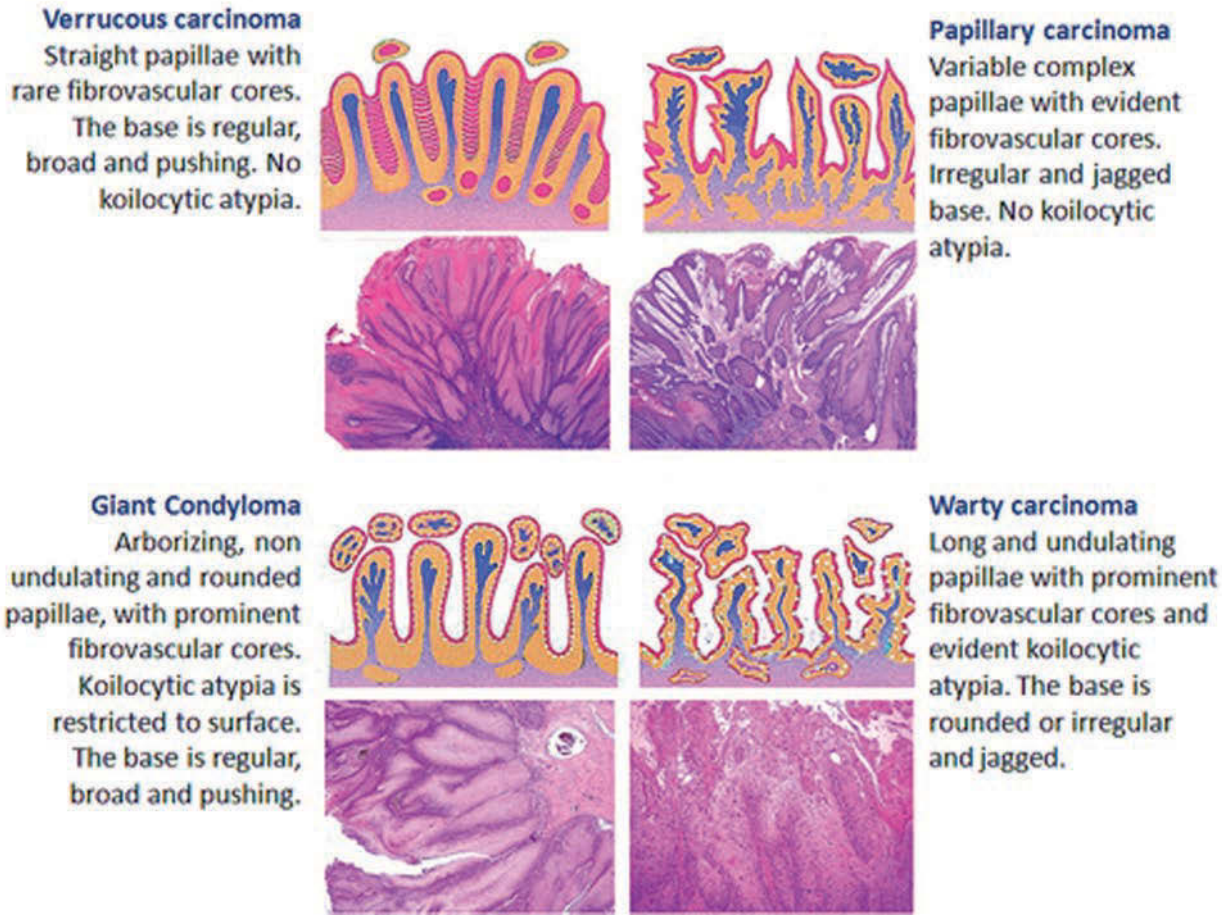

Fig. 6: *Differential diagnosis of verruciform penile tumors. The histopathological features that should be examined are the shape of the papillae, the presence of fibrovascular cores, the interphase between tumor and the underlying stroma and the presence of koilocytic atypia.*

Grossly, verrucous carcinomas are exophytic and papillomatous, varying from multinodular with cobblestone appearance to filiform with spiky appearance. The cut surface reveals a white serrated surface and a broadly based limit between tumor and stroma. Verrucous carcinomas are superficial, rarely penetrating beyond the lamina propria, superficial dartos or corpus spongiosum. Microscopically, there is extreme squamous differentiation except for occasional atypical nuclei at the basal or parabasal layers (Fig. 7). There are papillomatosis, hyper and orthokeratosis, acanthosis and a broadly based interphase between tumor and stroma, the latter feature a landmark of this tumor. Koilocytosis is not present. There is a spectrum of combined tumors with focal or significant verrucous features which need to be distinguished from typical verrucous carcinomas (Fig. 8). These mixed or hybrid verrucous carcinomas have a metastatic rate of about 25%.[29-31] Associated lesions are squamous (verrucoid) hyperplasia, differentiated penile intra-epithelial neoplasia (PeIN) and lichen sclerosus (Fig. 9).[32] An association with lichen planus hypertrophicus has been reported but since the number of cases is small a causal relationship is still speculative.[33]

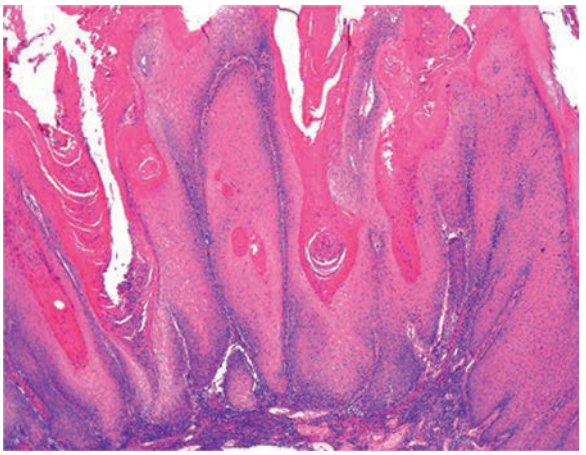

Fig. 7: *Verrucous SCC. The papillae are straight and lined by well differentiated neoplastic cells; there is surface hyperkeratosis and interpapillary keratin. The interphase between tumor and stroma is broad and pushing. No koilocytic changes are present.*

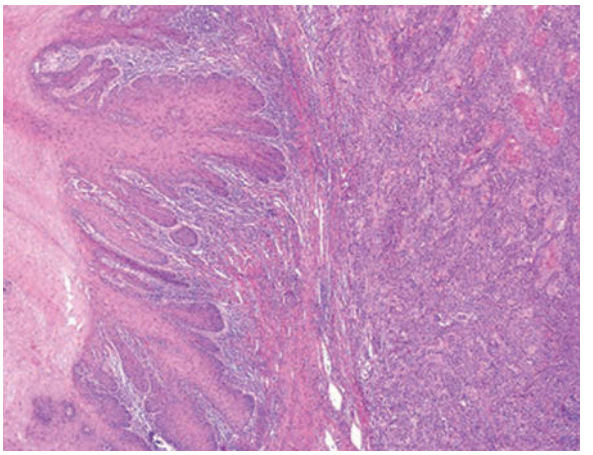

Fig. 8: *Mixed usual-verrucous SCC. The left field depicts a well differentiated verrucous carcinoma; in the right field a poorly differentiated usual SCC is evident.*

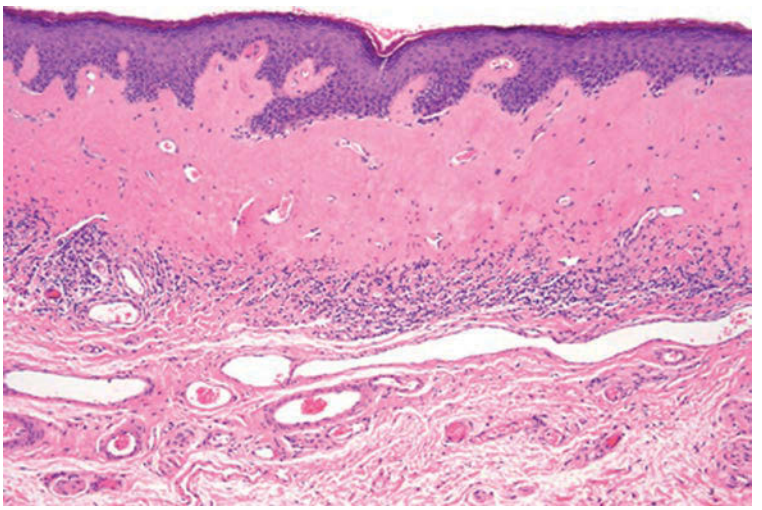

Fig. 9: *Lichen sclerosus. Beneath an atrophic squamous epithelium lies a uniformly dense collagen; a band of lymphocytic infiltrate is at the junction of lamina propria with preputial dartos.*

▪ Condylomatous (warty) carcinoma

Warty carcinomas are slow growing, verruciform low to intermediate grade HPV-related tumors, similar to giant condylomas but with a malignant histology and a potential for nodal metastasis. They account for 7% of all penile SCCs affecting patients younger than the usual SCC.[22,34]

Grossly they are cauliflower-like exophytic white gray tumors. The cut surface shows a papillomatous growth usually penetrating into corpora spongiosa and cavernosa (Fig. 10). The interphase of tumor and stroma is variable from broadly based to jagged and irregular. Microscopically, papillae are condylomatous with a prominent central fibrovascular core and koilocytic changes not restricted to the surface but also present in deep invasive portions of the tumor (Fig. 11). Hyper- and parakeratosis, cellular pleomorphism and clear cell features may be prominent (Fig. 12). There is a morphological spectrum of condylomatous tumors that share epithelial koilocytic changes ranging from clearly benign (usual condylomas) to frankly malignant (invasive warty carcinoma) passing through atypical condylomas and non-invasive warty carcinomas (Fig. 13).

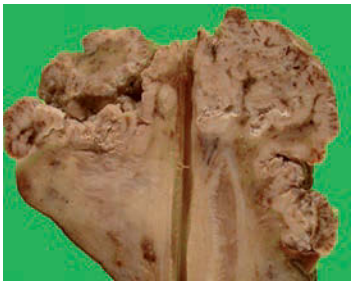

Fig. 10: *Warty SCC. A white-to-tan cauliflower-like exophytic tumor almost replacing the entire glans and invading up to near the tunica albuginea of the corpus cavernosum. The penile urethra is evident in the centre of the specimen.*

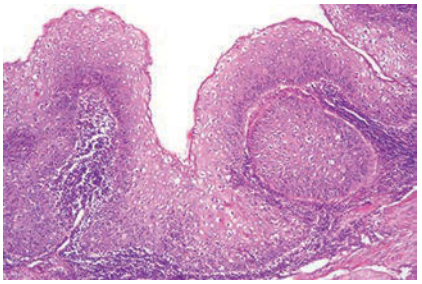

Fig. 11: *Warty SCC. Undulating papillae with fibrovascular cores; atypical koilocytic changes are evident through the full thickness of the neoplastic epithelium.*

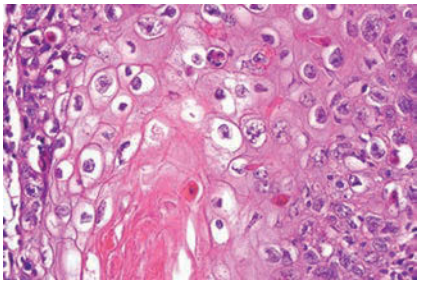

Fig. 12: *Warty SCC. Koilocytic atypia with nuclear wrinkling, perinuclear halos and multinucleation. Note also the atypical parakeratosis (lower left field) with dyskeratinocytes.*

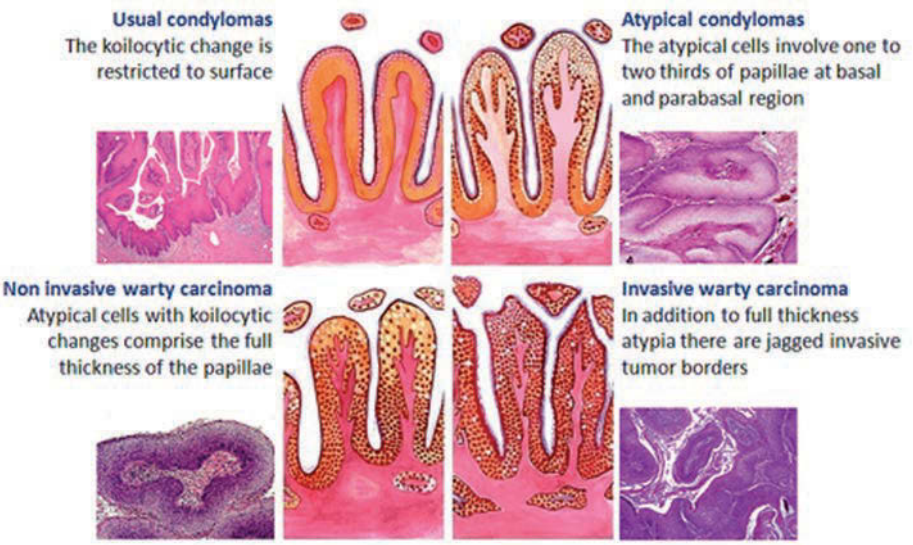

Fig. 13: *Morphological spectrum of condylomatous tumors, benign and malignant. All of them present epithelial koilocytic changes. Pathological distinctive features are the extension of the koilocytic atypia and the presence of stromal invasion.*

The biological behavior of warty carcinomas is intermediate between that of verrucous/papillary and SCC of the usual type. Deeply invasive, high-grade warty carcinomas may be associated with inguinal nodal metastases. The differential diagnosis is with verrucous and papillary carcinomas and with giant condylomas (Fig. 6). Warty carcinomas lack the extreme differentiation of verrucous carcinomas and unlike them they show jagged and irregular deep borders. Papillary carcinomas lack koilocytosis and typical condylomatous papillae and are extremely well differentiated. Associated precursor lesions of warty carcinomas are undifferentiated PeIN of the warty or basaloid types.

▪ Papillary carcinoma, NOS

Papillary carcinoma, NOS (not otherwise specified) is the third type of penile low-grade verruciform carcinoma, lacks distinctive diagnostic features and is not associated with HPV.[14] A diagnosis of papillary carcinoma is achieved after verrucous and warty carcinomas have been ruled out. Patients are about 60 years old. Grossly they are exophytic, large and irregular. The cut surface shows an invasive papillary neoplasm with irregular tumor front. Microscopically, the appearance is that of a well differentiated papillary squamous neoplasm (Fig. 14). There is hyperkeratosis and papillomatosis. Papillae are variable and complex, short or long, with or without a fibrovascu-

lar core. The tip is straight, undulated, spiky or blunt. Hyperkeratosis and acanthosis are prominent. The tumor front is irregular and infiltrative. Koilocytic-like changes are usually not present. Differentiating features from verrucous and warty carcinomas are based on the heterogeneity of the papillae, the lack of koilocytosis and the jagged irregular interphase between tumor and stroma. The latter feature is crucial to distinguish papillary from verrucous carcinoma (Fig. 6). HPV studies may be necessary to differentiate papillary neoplasms from low-grade warty carcinoma. Low-grade squamous intraepithelial lesions and lichen sclerosus are frequently associated with papillary carcinomas.[32] Papillary carcinomas are slow growing tumors with a low but definite incidence of inguinal nodal metastases.

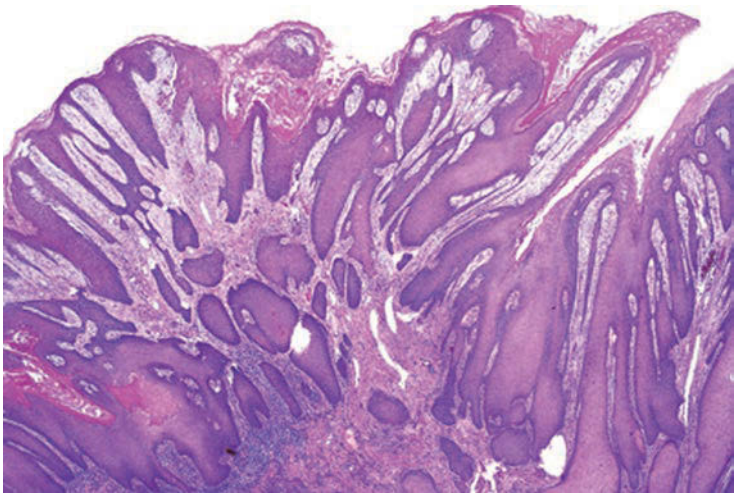

Fig. 14: *Papillary, NOS SCC. Complex papillae of variable morphology with and without fibrovascular cores; koilocytic changes are not usually found. The interphase between tumor and stroma is irregular and jagged.*

▪ Basaloid carcinoma

Basaloid carcinoma is an HPV-related tumor preferentially affecting the glans.[35] Rarely, it may originate in the foreskin. It accounts for 4% to 10% of penile SCCs. The median age is 53 years. More than half of patients show inguinal metastases at clinical diagnosis.

Grossly, there is an ulcerated non-exophytic irregular mass. The cut surface reveals a tan solid tumor, deeply invasive into the corpus spongiosum or cavernosum. Histologically, there are solid nests of small basaloid cells, usually with central necrosis (comedonecrosis) or central abrupt keratinization (Fig. 15). Nuclei are anaplastic and nucleoli inconspicuous. There are numerous mitotic figures. Penile intraepithelial neoplasia of the warty/basaloid type is often found in the epithelium adjacent to the invasive cancer.

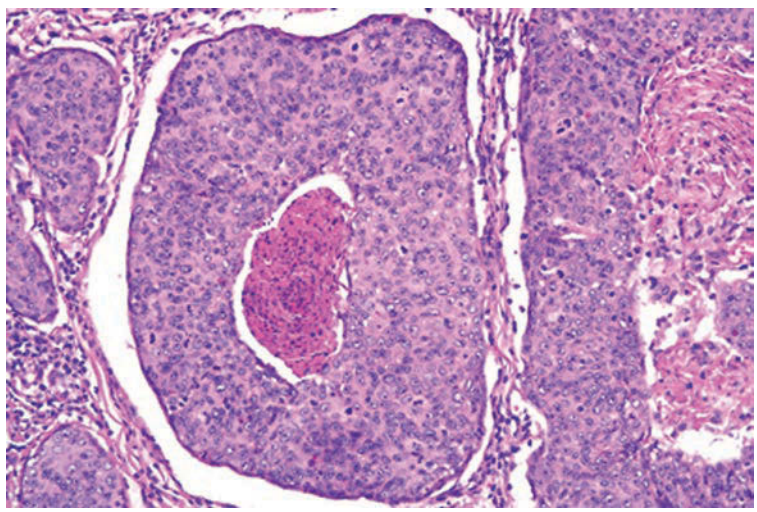

Fig. 15: *Basaloid SCC. Solid nests of anaplastic cells with abundant mitosis, abrupt keratinization and central necrosis ("comedonecrosis").*

▪ Sarcomatoid carcinoma

Sarcomatoid carcinomas are aggressive penile neoplasms predominantly composed of spindle cells.[36] They may arise *de novo,* after recurrence of a usual SCC or following irradiation therapy of a verrucous carcinoma. They account for about 1%-4% of all penile carcinomas. They involve preferentially the glans, but the foreskin may also be affected. Patients' mean age is around 60 years.

Grossly, they are bulky 5-10 cm ulcerated or rounded polypoid masses which on cut surface almost invariably deeply invade into the corpus cavernosum. Microscopically there are variable proportions of squamous cell and spindle cell carcinoma; usually the latter predominates (Fig. 16). The sarcomatoid component may mimic fibrous histiocytoma, leiomyosarcoma, fibrosarcoma, myxosarcoma or angiosarcoma. Heterologous bone and cartilaginous formation may be focally observed. Differential diagnosis is with sarcomas or malignant melanomas. Multiple sections and immunohistochemical studies may be necessary to make a correct diagnosis. The spindle cells are usually positive for vimentin, different cytokeratins and *p63*. In our experience, cytokeratin 34β-E12 and *p63* appear to be the more specific and sensitive markers to categorize these tumors as epithelial. Regional metastases occur in 85% of sarcomatoid carcinomas and mortality is high. In a series of 5 cases 80% of the patients presented with distant metastases affecting lung, skin, bone, pericardium and pleura.[37] We analyzed 5 cases for HPV using the *in situ* hybridization technique with negative results.[36] However, more recently DNA of HPV-16 and HPV-18 was identified in 2 patients with sarcomatoid carcinoma, suggesting an etiological role, at least in some cases.[38] The presence of HPV in sarcomatoid carcinoma may be related to the type of SCC giving origin to the neoplasm.

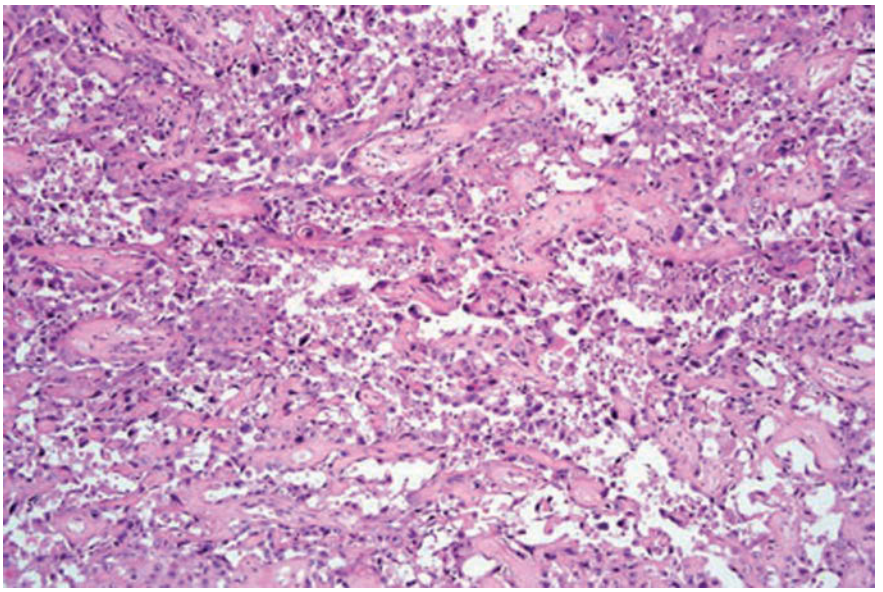

Fig. 16: *Sarcomatoid SCC. Highly anaplastic cells with a variegated morphology mimicking angiosarcoma.*

▪ Carcinoma cuniculatum

These are deeply penetrating albeit low-grade SCCs which, because of their burrowing growth pattern, were designated in the plantar region as epithelioma cuniculatum by Aird et al. in 1954.[39] Seven cases of this unusual variant of SCC were reported in the penis.[40] The mean patient age is 77 years. Grossly, the tumors are white gray exo-endophytic and papillomatous, affecting the glans and extending to the coronal sulcus and foreskin, with an average size of 6 cm. The hallmark of the lesion is noted on cut surface: deep invaginations of the tumor form irregular, narrow and elongated neoplastic sinus tracts that connect the surface tumor to deep anatomical structures (Fig. 17). Microscopically, the tumor morphology is that of a verrucous carcinoma with a bulbous front of invasion (Fig. 18). There may, however, be irregular foci of invasive SCC of the usual type. It should be distinguished from classical verrucous carcinoma, which is extremely well differentiated, rarely invades beyond the lamina propria and has a sharply delineated tumor front. Despite the deep penetration, none of the reported carcinoma cuniculatum cases showed groin metastases or systemic dissemination at the time of diagnosis.

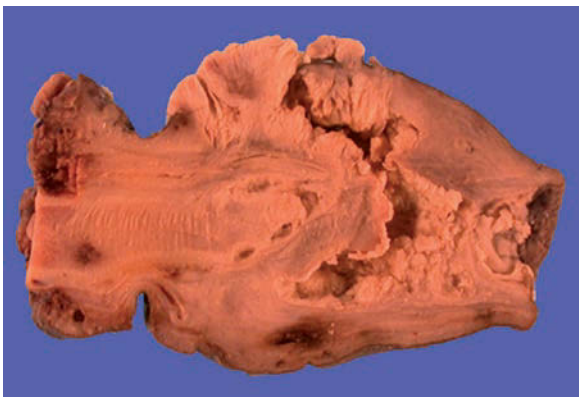

Fig. 17: *Carcinoma cuniculatum. Deeply infiltrating tumor composed of sinuses and interconnected tracts, simulating a rabbit's burrow (cuniculus). Note cystic-like foci within tunica albuginea.*

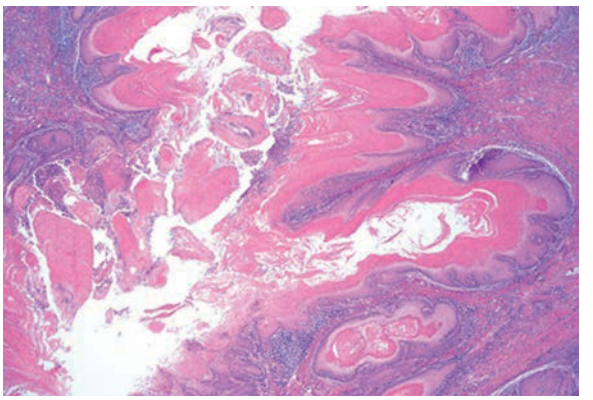

Fig. 18: *Carcinoma cuniculatum. Sinus tract of an extremely well differentiated SCC characterized by a deeply infiltrating verrucous proliferation with minimal atypia.*

▪ Pseudohyperplastic carcinoma

Pseudohyperplastic carcinoma is a clinicopathologic entity represented by a low-grade usual SCC preferentially affecting the foreskin of older patients (8th decade) in association with lichen sclerosus.[41] There is extreme differentiation and in small biopsies the tumors may mimic pseudoepitheliomatous hyperplasia. They are often multicentric and the second or third independent tumor may be verrucous. Grossly, they are flat or slightly elevated lesions measuring about 2 cm. Microscopically there are keratinizing nests of squamous cells with minimal atypia surrounded by a reactive stroma (Fig. 19). This degree of differentiation is noted only in low-grade verruciform tumors such as verrucous or papillary carcinomas. The consistent association with lichen sclerosus suggests that this inflammatory condition may play a pathogenic role. In a series of 10 cases, recurrence was noted in the glans of 1 patient who was circumcised for a multicentric carcinoma of the foreskin 2 years after diagnosis. No metastases were found in any of these cases.

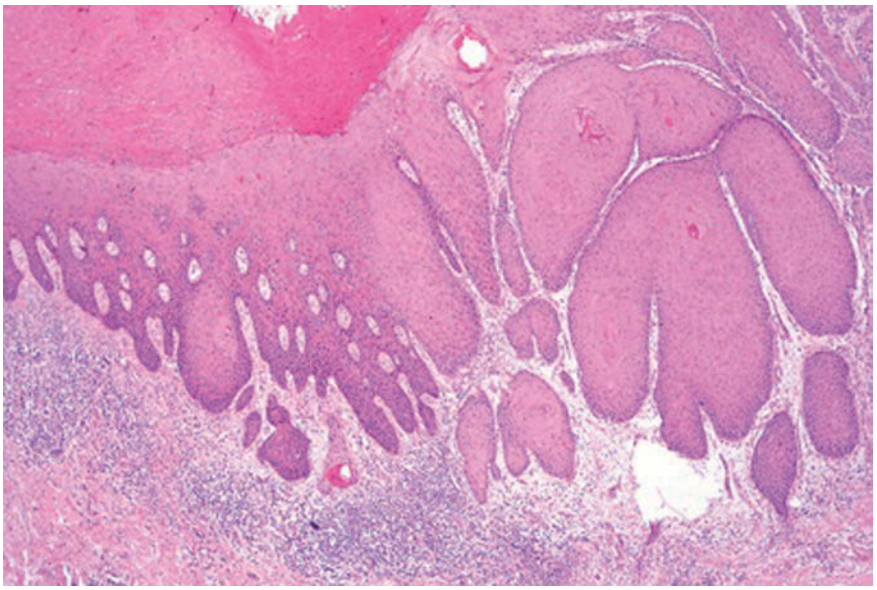

Fig. 19: *Pseudohyperplastic SCC low-grade tumor with a pseudoepitheliomatous appearance and a prominent chronic inflammation surrounding tumoral nests.*

▪ Clear cell carcinoma

Clear cell features may be noted in usual and warty SCCs. A distinctive aggressive penile tumor exclusively composed of clear cells and designated as clear cell carcinoma was recently reported from Austria.[42] Grossly they were large, exophytic, partially ulcerated and widely invasive, all located in the foreskin inner surface. Microscopically, there were large neoplastic cells with clear PAS positive cytoplasm (Fig. 20). HPV-16 was present in all reported cases. All 5 patients had groin cystic clear cell metastases. Two patients were reported as alive and the rest either dead or with evidence of disease at last follow-up.

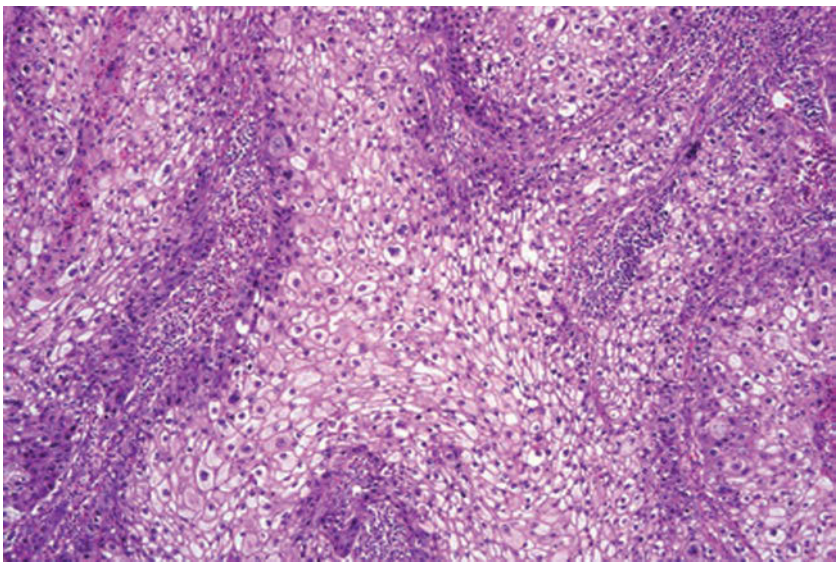

Fig. 20: *Clear cell SCC. Tumoral nests composed of polygonal cells with prominent clear cell cytoplasm and anaplastic nuclei.*

▪ Adenosquamous carcinoma

Adenosquamous carcinoma is a rare tumor composed of squamous cells with mucinous glandular differentiation. They are thought to arise from the epithelial surface of the glans, where foci of SCC *in situ* may be noted. Clinicopathologic features and outcome are similar to the usual SCC. Grossly a firm granular large neoplasm deeply invading the penile corpora is present. Microscopically there is a mixed squamous cell mucin-producing adenocarcinoma pattern (Fig. 21). The squamous component predominates.[43] The glands stain with carcinoembryonic antigen (CEA). Adenosquamous carcinomas should be distinguished from mucoepidermoid, adenobasaloid and pseudoglandular SCCs. In mucoepidermoid carcinomas, there are isolated cells or groups of squamous cells containing mucin without glandular formation.[44] In adenobasaloid tumors, there are well formed mucin secreting glands; however, the solid component is not the typical SCC, but a basaloid carcinoma. In pseudoglandular SCCs the lack of mucin production or the intraluminal presence of desquamated cell debris helps in the differential diagnosis. Another differential diagnosis is with adenocarcinoma arising in Littré glands. These tumors are ventrally located entirely glandular mucinous tumors. The few reported cases of adenosquamous carcinomas have behaved aggressively with frequent nodal metastases.

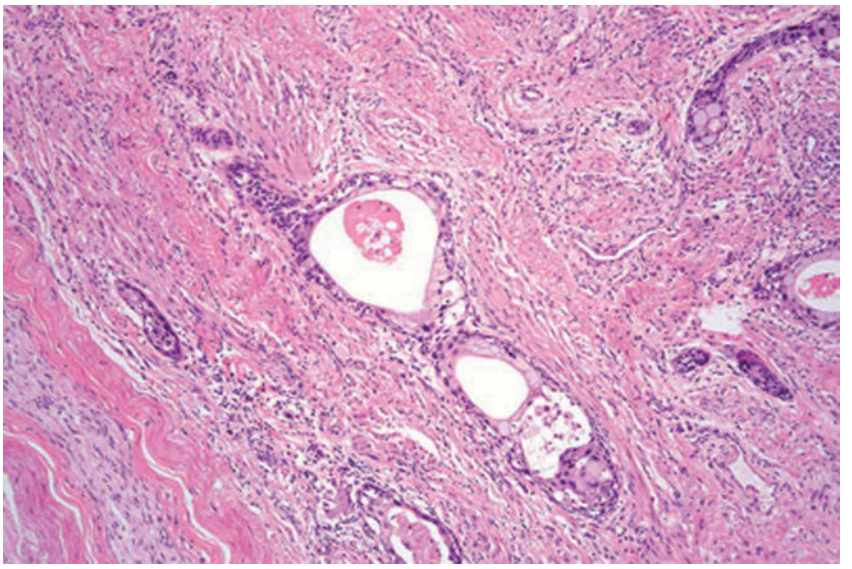

Fig. 21: *Adenosquamous SCC. Histological variant characterized by glandular differentiation within neoplastic nests of squamous appearance.*

▪ Acantholytic (adenoid, pseudoglandular) carcinoma

This is an unusual variant of SCC characterized by prominent acantholysis and formation of pseudoglandular spaces.[45] Patients' mean age is 54 years. Grossly they are large, irregular masses involving multiple penile anatomical compartments and deeply invading into erectile corpora. Microscopically the pseudoglandular spaces contain keratin, acantholytic cells and necrotic debris (Fig. 22); CEA and mucin stains are negative. Compared with the usual type, pseudoglandular SCCs show higher grade foci, invade deeper anatomical structures and are associated with a higher incidence of regional metastases and mortality. The differential diagnosis includes gland forming penile tumors (surface adenosquamous, mucoepidermoid and urethral adenocarcinomas) and the angiosarcomatoid variant of sarcomatoid carcinoma. Pseudoglandular carcinomas are aggressive with frequent nodal metastases.

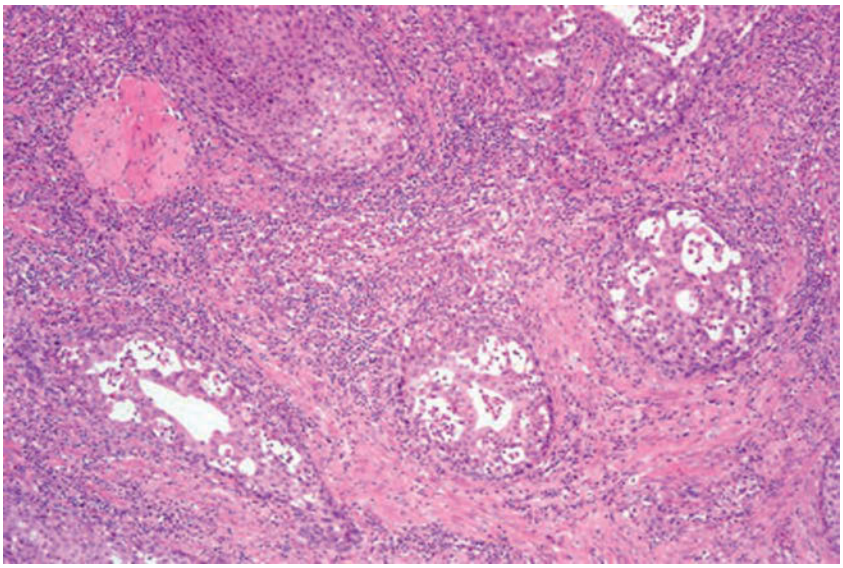

Fig. 22: *Acantholytic SCC. Tumoral nests exhibiting prominent acantholysis with pseudoglandular formation.*

▪ Giant condyloma

Described by Drs Buschke and Löwenstein[46] they are exophytic tumors reaching large sizes after years of evolution. There has been much confusion about the correct classification of these tumors. Patients are older than those with usual condylomas and younger than those with condylomatous (warty) carcinomas. Grossly, they are cauliflower-like tumors showing at cut surface a papillomatous growth with a sharp demarcation between tumor and stroma. The deep border may affect the lamina propria, dartos or corpus spongiosum. Microscopically they are exo-endophytic with features identical to usual condylomata (Fig. 23 and 24). Some cases harbor atypical cells and malignant transformation to an invasive SCC has been described in a rate of 30% to 42%.[47,48] The condylomatous papillae show a central fibrovascular core and superficial koilocytic changes. The differential diagnosis is with other verruciform (Fig. 6) and condylomatous (Fig. 13) tumors such as common condyloma and non-invasive warty carcinoma. Common condylomas affect younger patients, are smaller lesions and usually multiple, affecting not only the squamous epithelium of the penile mucosal epithelial compartments but also the outer surface of the foreskin and shaft. Giant condylomas affect older patients, are usually bulky and unicentric. The distinction of giant condylomas from well differentiated warty carcinomas may be difficult.[4,22]

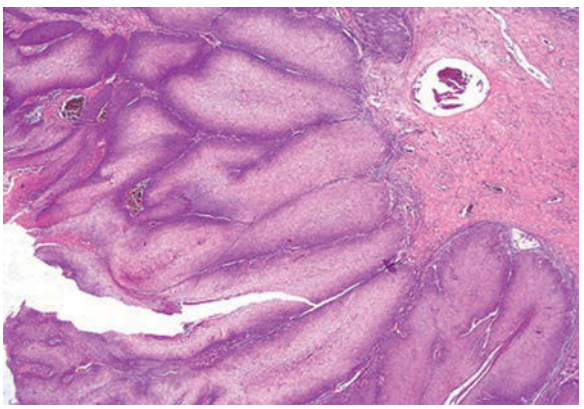

Fig. 23: *Giant condyloma. Rounded and undulating papillae with evident fibrovascular cores are distinctive features; koilocytic atypia is restricted to the surface. The interphase with the stroma is broad and pushing.*

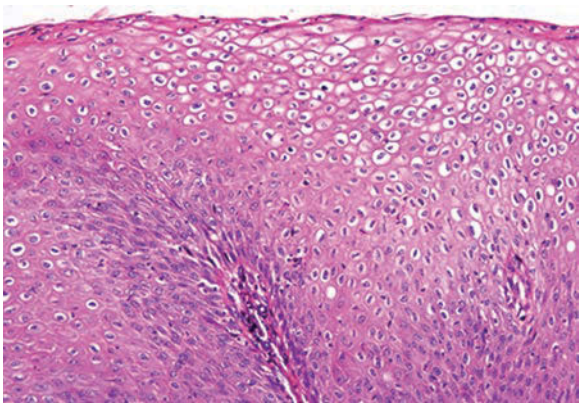

Fig. 24: *Giant condyloma. Koilocytic atypia, which occupies the upper third of the epithelium, consists of wrinkled hyperchromatic nuclei with perinuclear halos. Atypical parakeratosis is also present.*

Guidelines and recommendations for handling of the specimen, pathological margins and pathology report

Routine examination

Proper handling of the resected specimen requires a sound knowledge of the anatomical features of the penis. The glans and foreskin should be individually examined. The gross sequence for pathologic examination is: evaluation of the foreskin, section of the urethral and shaft margins and vertical longitudinal parallel sections of the penectomy specimen.

Circumcision specimen: Stretch and pin the specimen to a rectangular shape. Fix it for several hours or overnight in formalin. Include the entire mucosal and skin margins of resection. Cut serial vertical sections, labeling 1 to 12, clockwise. The tissue on the slide should show peripherally the skin, the mucocutaneous junction, the inner mucosal squamous epithelium and centrally all five histological layers.

Foreskin, coronal sulcus, and glans: if not involved by tumor, remove the foreskin, leaving a 2 to 3 mm redundant edge of foreskin around the sulcus. This permits better evaluation of the coronal sulcus. If tumor originates in the sulcus, a wider margin of foreskin may be left. Proceed with the foreskin as indicated above.

Glans: Cut vertically first at the central area (use the meatus and proximal urethra as reference points), separating the specimen into two halves. Then cut three to six serial sections, 2 to 3 mm in width, from each half. The central section should include from surface to deep areas: the epithelium, lamina propria, corpus spongiosum, tunica albuginea and corpora cavernosa. This method of sectioning permits easy orientation of the complex anatomy of the penis, and facilitates the reconstruction of the lesion in a diagram.

Resection margins: include a shaft margin and a urethral margin, which should be submitted in every case; routes of local spread of penile SCC should be considered for proper tissue submission (Fig. 25). Shaft margin: divide it in two along the central septum or median raphe; the cut surface should include the skin of the shaft, dartos, Buck's fascia, tunica albuginea, and corpus cavernosum. Urethral margin: a transverse section should include the mucosal surface, surrounding lamina propria, and corpus spongiosum; in larger specimens it is important to submit two or three additional sections of the more distal urethral cylinder to ensure the adequacy of the resection margin, ruling out urethral or periurethral involvement by carcinoma (Fig. 26).

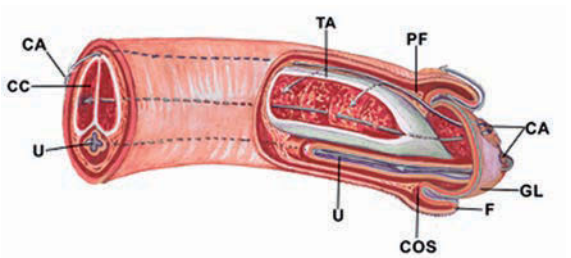

Fig. 25: *Local routes of spread of penile SCC. Tumors invade through the penile fascia (upper arrow), the corpora cavernosa (middle arrow) or the penile urethral mucosa (lower arrow). GL: glans; F: foreskin; CA: carcinoma; PF: penile fascia; TA: tunica albuginea; U: urethra; COS: coronal sulcus; CC: corpus cavernosum.*

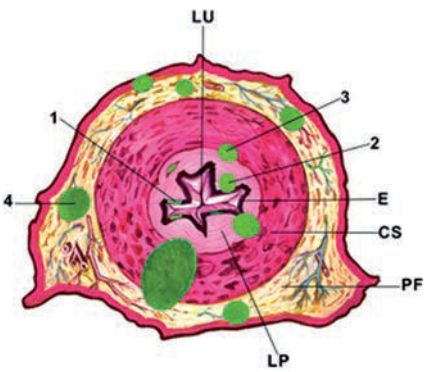

Fig. 26: *Anatomical sites of margin involvement in penile SCC are shown as green dots. Tumor can be found in the epithelium (1) or lamina propria (2) of the penile urethra, permeating the surrounding corpus spongiosum (3) or at the level of Buck's fascia (4).*

Frozen section evaluation of resection margins at time of circumcision or penectomy

Circumcision specimen: the entire circumference and thickness of the mucosal margin of resection should be submitted for frozen section evaluation. The specimen should be oriented with the coronal sulcus borders up.

Partial penectomy specimen: separate periurethral and shaft margins. The most common site of involvement by carcinoma is the cylinder composed of the periurethral corpus spongiosum, lamina propria, and urethral epithelium. The entire urethral lumen may be occluded by invasive carcinoma extending from the glans. Infiltrating cancer can involve the lamina propria, especially lymphatics or perineural spaces.[7] When the corpus spongiosum is involved, tumor nests are present in vascular spaces or in intervascular fibrous stroma. One frozen section usually suffices to study all these periurethral structures. Buck's fascia may be involved by carcinoma in the shaft at the time of surgery. Two to four sections are needed to study the cut surface of the shaft.

Total penectomy specimen: Only the urethra and the periurethral tissues should be frozen for margin evaluation during the operation. In these cases, or when the lesion is grossly near the skin margin, frozen sections of the entire skin circumference may be appropriate.

Pathology report: The final pathology report of carcinoma is based on information obtained from resected specimens[49] and should contain the following information:[50]

1) Histological type and subtype;
2) tumor site;
3) size (in cm);
4) pattern of growth;
5) histological grade (1-3);
6) anatomic levels of invasion;
7) depth of invasion (in mm);
8) vascular invasion;
9) perineural invasion;
10) margins of resection;
11) associated precancerous lesions;
12) other lesions associated (lichen sclerosus, dermatitides, etc).

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WHO histological classification of tumors of the penis	
I)	**Malignant epithelial tumors of the penis** Squamous cell carcinoma Basaloid carcinoma Warty (condylomatous) carcinoma Verrucous carcinoma Papillary carcinoma, NOS Sarcomatous carcinoma Mixed carcinomas Adenosquamous carcinoma Merkel cell carcinoma Small cell carcinoma of neuroendocrine type Sebaceous carcinoma Clear cell carcinoma Basal cell carcinoma
II)	**Precursor lesions** Intraepithelial neoplasia grade III Bowen's disease Erythroplasia of Queyrat Paget's disease
III)	**Melanocytic tumors** Melanocytic nevi Melanoma
IV)	**Mesenchymal tumors**
V)	**Haematopoietic tumors**
VI)	**Secondary tumors**

Committee 3

Penile Cancer – Prevention and Premalignant Conditions

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Penile Cancer - Prevention and Premalignant Conditions

Penile Cancer – Prevention and Premalignant Conditions

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Introduction

There is relatively little evidence available in the literature on the subject of the prevention of penile cancer and pre-malignant conditions of the penis.

The association of human papillomavirus (HPV) subtypes and penile cancer is however established, although the aetiology, natural history and treatment of such lesions are only reported in small series of patients with a relatively short follow-up period. The majority of these studies are retrospective case series.

Some of the options for prevention of penile cancer include circumcision, reducing the risk of transmission of penile HPV infections, prevention and early treatment of phimosis, smoking cessation and hygienic measures. The exact pathological role of chronic inflammatory conditions such as balanitis xerotica obliterans (BXO) in the aetiology of penile cancer remains largely unknown.

The recommendations in this chapter are based on the current evidence available in the literature. For the purposes of this consultation, this review is divided into four sections:

SECTION I

Epidemiology and demographics of penile cancer

Introduction

Penile cancer belongs to the rare male cancers. Although in western countries the incidence of penile cancer is very low (0.1 to 0.9/100.000 men in Europe) in some countries the incidence is significantly higher and penile cancer accounts for up to 10% of all male malignancies. For example, in Uganda and Paraguay the incidence is as high as 4.4 or 4.2/100.000 men.[1,2] Diagnosis of penile cancer influences survival substantially. Rippentrop et al.[3] observed a tumor related death rate of 41.4% and a mean survival of 66.8 months in carcinoma in situ (CIS), and a mean survival of 7.3 months in patients with distant metastases.

Risk and preventive factors

Penile cancer has been associated with a number of established risk factors and associated diseases or conditions. Phimosis with chronic inflammation, HPV infection, poor hygiene or smoking are most commonly described risk factors. On the other hand circumcision, HPV vaccination and improved genital hygiene may prevent penile cancer (Table 1).[4-6]

Table 1: Risk factors for the development of penile cancer	Preventive factors
Phimosis Smegma retention Chronic balanoposthitis HPV infection Penile oral sex[6] Lifetime number of female sex partners[6] Lifetime intercourse[6] Priapism[6] Poor genital hygiene Smoking Urethral stricture PUVA therapy	Circumcision HPV vaccination Cessation of smoking Therapy of genital inflammation Hygiene education Alcohol absence[6] Shielding PUVA

▪ Circumcision – routine neonatal

Circumcision has been performed for thousands of years, exclusively for ritual reasons in a number of cultures. Several other factors may also determine circumcision rates, including cultural factors and parental choice. Estimations suggest a circumcision rate of more than 25% of all males worldwide.[7] Up to the year 1999, the American Academy of Pediatrics[8] recommended routine neonatal circumcision for health related reasons. The rationale for the recommendation was a reduced rate of infant urinary tract infection. The prevention of phimosis may lead to a reduced risk of balanoposthitis and upper urinary tract infections, especially in patients with vesicoureteric reflux. Circumcision as a measure to prevent penile cancer has been repeatedly advocated by different authors. The logic for this is that in men undergoing routine neonatal circumcision the rate of penile cancer is significantly lower than in men with no history of circumcision.

Morris[6] advocates circumcision as a biomedical imperative for the 21st century, not only for the reduction of penile cancer by more than 20-fold, but for a decrease in urinary tract infections, inflammatory dermatoses and sexually transmitted diseases. Recent studies have suggested that phimosis and balanoposthitis are responsible for the development of penile cancer, and the reduced rate of penile cancer is mainly explained by the effective reduction of phimosis/balanoposthitis, smegma retention, and lichen sclerosus in comparison to non-circumcised men.

Daling et al.[9] conducted a population-based case-control study in western Washington state that included 137 men diagnosed with in situ (n=75) or invasive (n=62) penile cancer between 1979 and 1998, and 671 control men (Table 2). They could confirm other studies, as they found that men not circumcised in childhood had a 1.5-fold increased risk for developing penile cancer. As a result of this study they concluded that circumcision in early childhood may help prevent penile cancer by eliminating phimosis and preventing cofactors such as HPV infection.

Table 2: Risk of penile cancer associated with selected characteristics, stratified to circumcision status								
	Circumcision in childhood			Never circumcised			Circumcised later	
	Controls (n=392) n (%)	Cases (n=64) n (%)	Odds ratio (OR) (95% confidence interval (CI))	Controls (n=247) n(%)	Cases (n=60) n (%)	OR (95% CI)	Controls (n=31) n (%)	Cases (n=11) n (%)
Age (years)								
<50	173 (44.1)	28 (43.8)	-	30 (12.1)	7 (11.7)	-	3 (9.7)	1 (9.1)
50-64	154 (39.3)	23 (35.9)	-	118 (47.8)	24 (40.0)	-	17 (54.8)	5 (45.5)
65 +	65 (16.6)	13 (20.3)	-	99 (40.1)	29 (48.3)	-	11 (35.5)	5 (45.5)
Lifetime number of female sex partners								
1-4	155 (40.2)	13 (20.3)	≥1.0	118 (49.0)	27 (45.8)	≥1.0	10 (32.3)	5 (45.5)
5-14	124 (32.1)	20 (31.3)	1.8 (0.9-3.9)	59 (24.5)	14 (23.7)	0.9 (0.4-1.8)	13 (41.9)	5 (45.5)
15-*-	107 (27.7)	31 (48.4)	3.2 (1.5-6.4)	64 (26.6)	18 (30.5)	1.0 (0.5-2.0)	8 (25.8)	1 (9.1)
Smoking								
Never	135 (34.4)	16 (25.0)	≥1.0	79 (32.0)	9 (15.0)	≥1.0	10 (32.3)	2 (18.2)
Former	174 (44.4)	20 (31.3)	0.8 (0.4-1.7)	113 (45.7)	34 (56.7)	2.8 (1.2-65)	7 (22.6)	2 (18.2)
Current	83 (21.2)	28 (43.7)	2.2 (1.1-4.5)	55 (22.3)	17 (28.3)	3.1 (1.2-8.0)	14 (45.2)	7 (63.6)
Genital warts								
No	367 (93.6)	43 (68.3)	≥1.0	241 (98.0)	47 (78.3)	≥1.0	30 (96.8)	9 (81.8)
Yes	25 (6.4)	20 (31.7)	6.7 (3.2-14.0)	5 (2.0)	13 (21.7)	13.3 (4.3-41.3)	1 (3.2)	2 (18.2)
HSV-2 serology								
Negative	281 (84.9)	33 (57.9)	≥1.0	184 (86.8)	36 (64.3)	≥1.0	22 (78.6)	6 (75.0)
Positive	50 (15.1)	24 (42.1)	3.0 (1.5-4.8)	28 (13.2)	20 (35.7)	3.4 (1.6-7.1)	6 (21.4)	2 (25.0)
HPV 16 serology								
Negative	295 (86.8)	37 (66.1)	≥1.0	189 (88.7)	46 (83.6)	≥1.0	24 (85.7)	8 (100.0)
Positive	45 (13.2)	19 (33.9)	2.6 (1.3-5.1)	24 (11, 3)	9 (16.4)	1.5 (0.6-3.5)	4 (14.3)	0 (0.0)
Gonorrhea								
Never	358 (91.3)	51 (79.7)	≥1.0	233 (94.3)	52 (88.1)	≥1.0	20 (64.5)	9 (90.0)
Ever	34 (8.7)	13 (20.3)	1.7 (0.8-3.8)	14 (5.7)	7 (11.9)	2.2 (0.8-6.3)	11 (35.5)	1 (10.0)
Nongonoccocal urethritis								
Never	360 (92.5)	53 (82.8)	≥1.0	236 (95.9)	56 (93.3)	≥1.0	27 (90.0)	11 (100.0)
Ever	29 (7.5)	11 (17.2)	1.9 (0.8-4.2)	10 (4.1)	4 (6.7)	1.4 (0.4-4.9)	3 (10.0)	0 (0.0)
Urinary tract infection								
Never	329 (84.1)	51 (79.7)	≥1.0	199 (81.2)	46 (76.7)	≥1.0	25 (80.7)	7 (63.6)
Ever	62 (15.9)	13 (20.3)	15 (0.8-3.1)	46 (18.8)	14 (23.3)	1.5 (0.7-3.0)	6 (19.4)	4 (36.4)

Phimosis								
No	-	-	-	237 (96.3)	41 (68.3)	≥1.0	17 (58.6)	4 (40.0)
Yes	-	-	-	9 (3.7)	19 (31.7)	15.7 (6.0-41.1)	12 (41.4)	6 (60.0)
Smegma								
Never/rarely	-	-	-	239 (97.1)	54 (90.0)	≥1.0	24 (82.8)	9 (100.0)
Sometimes/ usually	-	-	-	7 (2.9)	6 (10.0)	4.0 (1.2-13.0)	5 (17.2)	0 (0.0)
Penile tear								
No	359 (91.6)	53 (82.8)	≥1.0	236 (95.5)	42 (70.0)	≥1.0	29 (93.5)	5 (45.5)
Yes	33 (8.4)	11 (17.2)	2.1 (1.0-4.7)	11 (4.5)	18 (30.0)	12.5 (5.0-31.1)	2 (6.5)	6 (54.5)
Penile rash								
No	384 (98.0)	51 (79.7)	≥1.0	244 (98.8)	47 (78.3)	≥1.0	30 (96.8)	8 (72.7)
Yes	8 (2.0)	13 (20.3)	9.5 (3.6-24.9)	3 (1.2)	13 (21.7)	23.2 (5.9-90.4)	1 (3.2)	3 (27.3)
Penile injury								
No	381 (97.2)	58 (90.6)	≥1.0	238 (96.4)	55 (91.7)	≥1.0	31 (100.0)	9 (81.8)
Yes	11 (2.8)	6 (9.4)	3.5 (1.2-10.6)	9 (3.6)	5 (8.3)	2.3 (0.7-7.4)	0 (0.0)	2 (18.2)
Penile inflammation								
No	387 (99.0)	58 (90.6)	≥1.0	240 (97.2)	55 (93.2)	≥1.0	29 (93.5)	11 (100.0)
Yes	4 (1.0)	6 (9.4)	7.9 (2.0-31.0)	7 (2.8)	4 (6.8)	2.6 (07-9.7)	2 (6.5)	0 (0.0)
Urethral stricture								
No	375 (95.7)	57(91.9)	≥1.0	227 (92.7)	53 (88.3)	≥1.0	27 (90.0)	8 (72.7)
Yes	17 (4.3)	5 (8.1)	1.8 (0.6-5.2)	18 (7.3)	7 (11.7)	1.5 (0.6-4.0)	3 (10.0)	3 (27.3)

From Daling et al.[9] (this

▪ Smoking

Smoking was repeatedly described to have a consistent association to penile cancer. Harish and Ravi[10] found a significant association between smoking or chewing tobacco and penile carcinoma. They compared 503 men and age matched controls. In multivariate analysis a significant association was found as well as a dose-dependent relationship. Dillner et al.[11] reviewed the epidemiology of invasive cancer of the penis based on scientific publications identified by a Medline search from 1966–2000 for the keywords penis/penile, cancer/carcinoma and risk as well as the cited references in the identified papers. A consistent association was found between penile cancer and smoking habits. The risk was dose-dependent and not explained by investigated confounding factors such as phimosis and sexual history.

Daling and coworkers[9] found an odds ratio (OR) of 2.3 according to active smoking status. The HPV status did not alter the increased OR for smokers in contrast to non-smokers. Former smokers had an OR of 1.9 e.g. 1.4 and current smokers an OR of 2.6 and 2.8 for HPV+ and HPV- cases. On the other hand, current smokers had a considerably increased OR (4.5) for invasive cancer, that differed noticeably from the moderately increased risk for former smokers or the moderately increased risk for in situ penile cancer (Table 3).

Table 3: Risk of penile cancer associated with selected risk factors, stratified by extent of disease

Characteristic	Controls (n=671) N (%)	In situ cases (n=75)		Invasive cases (n=62)	
		N (%)	OR (95% CI)	N (%)	OR (95%CI)
Age at reference date (years)	-	-	-	-	-
<50	205 (30.5%)	21 (28.0%)	-	15 (24.2%)	-
50 – 64	291 (43.4%)	25 (33.3%)	-	27 (43.5%)	-
65+	175 (26.1%)	29 (38.7%)	-	20 (32.3%)	-
Smoking	-	-	-	-	-
Never	224 (33.4%)	19 (25.3%)	≥1.0	9 (14.5%)	≥1.0
Former	301 (44.9%)	36 (48.0%)	1.3 (0.7 – 2.4)	25 (40.3%)	1.8 (0.8-3.9)
Current	146 (21.8%)	20 (26.7%)	1.5 (0.7-2.9)	28 (45.2%)	4.5 (2.0-10.1)

from Daling et al.[9]

▪ Human papillomavirus (HPV) infection

Some studies could show an association between HPV infection and penile cancer comparable to cervical cancer, where high risk HPV infection plays a very important role. In cervical cancer, HPV infection was considered responsible for nearly all cancers. In penile cancer the role of high risk HPV infection seems to be variable and is not clear. Some authors divide penile cancer in HPV+ and HPV- cases. Nevertheless, there are some studies of the relationship between HPV infection and penile cancer. Cupp et al.[12] detected HPV in 55% of their 46 penile cancer cases by PCR technique. The rate of HPV infection reported by Sarkar et al.[13] was even higher at 81.8%. Senba and coworkers[14] studied 88 specimens of penile cancer in Thailand. They detected HPV DNA in 81.5% using PCR. The most prevalent HPV type was HPV 18 (55.4%), followed by HPV 6 (43.1%). Scheiner et al.[15] determined the prevalence of HPV in Rio de Janeiro, Brazil, in 80 consecutive cases and found HPV DNA in 75% of patients with invasive carcinoma and 50% with verrucous carcinomas.

In contrast to healthy controls the HPV infection rate differed markedly. The seropositivity to HPV

16, HPV 18, or HPV 45, the most common oncogenic types of HPV, was 46% among penile cancer cases and 12% among controls (OR 5.0; 95% CI (confidence interval) 1.4-17.2) in a case-control study in Uganda.[16] Positive HPV 16 serology was found among 24% of cases and 12% of controls in a North American case-control study (OR 1.9; 95% CI 1.2-3.2) and 80% of penile cancer tissue specimens were positive for HPV DNA.[9]

The aggressiveness and influence on prognosis of penile cancer has been investigated by several authors. No correlation could be found by Wiener et al.[17] and Bezerra et al.[18] In contrast, Gregoire et al.[19] described a more aggressive vertical tumor growth and more poorly differentiated cancers. Daling et al.[9] also found an increased risk for invasive cancers with HPV+ 16 serology.

▪ Background information to HPV vaccination

HPV is an uncoated double chain DNA-virus. It belongs to the family of the papova viruses and is composed of two so-called L1 and L2 capsides. There are more than 100 known variants of HPV. Muñoz et al.[20] classified HPV types according to their oncogenic potential (Table 4).

Table 4: HPV types and oncogenic potential

Classification	HPV types
High risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably oncogenic	26, 53, 66, 68, 73, 82
Low risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81

Modified from Muñoz et al.[20]

In gynaecological oncology it is well established that persisting HPV infection leads to cervical cancer with a latency period of 8 to 10 years. Recently, two vaccines against the most frequent high risk HPV types (HPV 16 and 18) have been developed - Gardasil®, a quadrivalent vaccine targeting HPV 6, 11, 16 and 18, and Cervarix®, a bivalent vaccine which targets HPV 16 and 18. HPV 16 and 18 are most commonly associated with cervical cancer and the vaccination could prevent nearly 70% of all cervical cancers. As there is a different distribution of HPV types world-wide, the preventive effect is restricted to countries with predominantly HPV 16 and HPV 18 infections. HPV types 16, 18, 31 and 45 are leading in Europe and US, whereas in South America HPV types 13, 33, 39 and 59 are the most common high risk HPV types.

▪ HPV vaccination in males

The approval studies for HPV vaccines included some boys from 9 to 15 years of age. The rate of seroconversion after vaccination was comparable to girls and as high as 99.1 to 100%. The anti-HPV immunoreaction after vaccination was higher in boys and girls than in women. The protection from HPV infection is secure up to 5 years after vaccination. Further long-term data are currently not available.[21] In the absence of data regarding male vaccination one can only assume that male vaccination could prevent HPV associated penile cancer development. If there is a decision for HPV vaccination, for example by parental choice, male vaccination should be performed as in girls before the first sexual contact. Penile cancer is not exclusively restricted to HPV infection, but is also associated with chronic inflammatory processes like phimosis, balanoposthitis or lichen sclerosus, therefore HPV vaccination can not be an absolute guarantee for prevention of penile cancer.

Further open questions are:

- Vaccination of special risk groups (men with multiple partners)
- Vaccination in countries with high prevalence

of penile cancer and predominant HPV 16 or HPV 18 infections
- Partners from patients with genital warts or other sexually transmitted disease (STD)
- Boys from high risk groups.

▪ Condom use

As about 50% of penile cancer is due to HPV infection, the avoidance of HPV transmission between sexual partners may lead to a reduction of penile cancer incidence. Few papers are available on the effect of condom use in the prevention or therapy of HPV infection. A paper assessing the use of condoms was published by Wen and coworkers[22] in 1999. In this retrospective case-control study of nearly 1000 patients, the authors were able to demonstrate a protective effect of condom use in patients with genital warts. In both sexes, failure to use condoms was independently associated with an increased risk of acquisition of genital warts, and consistent condom use was associated with a decreased risk of acquisition of genital warts (Table 5).

Table 5: Risk of genital warts in relation to condom use

Condom use	Cases No (%)	Controls No (%)	Adjusted OR (95% CI) *
Men (1) (X_4^2 = 62.3, p<0.001)			
Not applicable, no sex	78(13.0)	52 (11.6)	1
Never	195(32.4)	80 (17.9)	1.9 (1.3-2.9)
Sometimes <50%	89 (14.8)	41 (9.2)	3.0 (2.2-4.3)
Usually >50%	81(13.5)	52(11.6)	0.9(0.7-2.0)
Always (100%) excluding breakages	159(26.4)	222(49.4)	0.7(0.3-0.9)
			p<0.0001
Women (2) (X_4^2= 15.2, p=0.004)			
Not applicable, no sex	34 (10.8)	23 (9.9)	1
Never	91 (28.9)	63 (27.0)	1.8 (0.9-3.6)
Sometimes <50%	59 (18.7)	22 (9.4)	1.7 (1.0-2.9)
Usually >50%	54 (17.1)	38(16.3)	0.8 (0.7-1.7)
Always (100%) excluding breakages	77 (24.4)	87 (37.3)	0.7 (0.4-1.0)
			p=0.013

*Multivariate logistic regression with variables shown to be associated with genital warts in univariate analysis: (1) Age group, number of lifetime sex partners, and smoking; (2) age group, marital status, and occupations. OR = odds ratio, CI = confidence interval.
From Wen et al.[22]

In a follow-up study of 82 female university students, Winer and coworkers[23] showed that in newly sexually active women, consistent condom use by their partners appeared to reduce the risk of cervical and vulvovaginal HPV infection. In addition, in couples who reported 100 percent condom use, no cervical squamous intraepithelial lesions could be observed, in contrast to couples without condom use. Bleeker et al.[24] performed a randomized trial with couples in which women had cervical intraepithelial neoplasia and their male partner had HPV associated flat lesions of the penis. Couples were randomized for the use of a condom. In this study, men in the condom use group experienced a significantly reduced time to regression of the flat lesion of the penis. The effect of the described phenomenon is probably due to the blocking of viral transmission

between the sexual partners. The same group[25] showed in another study that in couples infected by the same HPV type the use of condoms led to the regression of flat penile lesions, whereas in couples with HPV non-concordance a significant effect of condom use could not be observed.

▪ Phimosis

Phimosis is a condition where the male foreskin cannot be retracted. It is physiological in the first few years of life. Physiological phimosis can persist and appear as a narrowness of the foreskin, fusion of the foreskin with the glans or by frenulum breve (short foreskin). On the other hand, phimosis can be acquired. Frequent causes of acquired phimosis are chronic inflammation, balanoposthitis, forceful foreskin retraction, lichen sclerosus or diabetes mellitus. The prevalence of phimosis differs regionally from 8% to 23% (Table 6). It has to be kept in mind that definitions of phimosis and time of diagnosis may differ from study to study.

Table 6: Incidence of phimosis

Population	Incidence	References
British, aged 5-13	20%	Gairdner, 1949[26]
Danish, aged 8	8%	Oster, 1968[27]
British soldiers	14%	Osmond, 1953[28]
German youths	9%	Saitmacher, 1960[29]
German men	9%	Schöberlein, 1976[30]
Japanese, aged 11-15	23%	Ishikawa and Kawakita, 2004[31]
Taiwanese, aged 13	16%	Ko et al. 2007[32]

From Morris[6]

Tseng et al.[33] performed a population based case-control study in Los Angeles County with 100 matched case-control pairs. Phimosis was strongly associated with penile invasive cancer. Although they found an inverse correlation between penile cancer and neonatal circumcision, the correlation was appreciably weakened when the analysis was restricted to subjects with no history of phimosis. The authors concluded that the protective effect of neonatal circumcision is largely mediated by prevention of phimosis.

▪ Infection

Balanitis and posthitis are inflammation of the glans and prepuce. The incidence differs between circumcised (11%–13%) and uncircumcised men (2%). Dillner et al.[11] reported a Swedish case-control study of 244 patients, 45% of whom had had at least one episode of balanitis, compared with 8% among controls. A special risk group for balanitis is diabetics, where balanitis is seen in 35%.

▪ Chronic inflammatory conditions, lichen sclerosus et atrophicus

Lichen sclerosus (LS) et atrophicus and balanitis xerotica obliterans (BXO) are synonymous. LS is a chronic inflammatory skin disorder, restricted to the glans and foreskin with a prevalence of below 1% in childhood. LS may occur in skin already scarred or damaged, and trauma and injury have also been suggested as triggers. An autoimmune pathogenesis after infection is also suggested. In addition, phimosis is often associated with LS. Kiss et al.[34] as well as Yardley et al.[35] found LS in their circumcision specimens in 40% and 34.5%. Nasca et al.[36] evaluated HPV prevalence in paraffin embedded penile specimens from 46 men with LS and in brush cytology of a randomly selected control group. They detected about

twice as much HPV infections in patients with LS (17.4%) compared to healthy controls (8.7%). The authors concluded that high risk HPV infection in patients with LS may enhance the risk of penile cancer arising on LS.

Prowse et al.[37] analysed penile cancer and LS lesions in 46 men for HPV status. In 54% of cancers and in 33% of LS cases HPV 16 could be detected. Barbagli et al.[38] performed an observational descriptive study. They reviewed histology of 130 patients with LS to determine the presence of premalignant and malignant lesions and reported that 11 of 130 (8.4%) showed premalignant or malignant histopathological changes. They concluded that patients with LS should be followed up closely. The incidence of LS is described to be 2.3% to 5.8% in other studies.[39, 40] Studies suggest that patients with squamous cell carcinoma (SCC) have much higher rates of preexisting LS. Powell et al.[41] found preexisting LS in 10 of 20 patients with SCC. Pietrzak et al.[42] reviewed 155 patients with penile carcinoma. They found LS in 28% of men with penile cancer. Perceau et al.[43] demonstrated that 44% of penile SCC were associated with LS. The authors found that non-LS associated penile SCC tended to be associated with high risk HPV infection whereas non-LS associated penile SCC was not, although this was a retrospective study with small numbers of patients.

Von Krogh and Horenblas[44] have stated that no consensus has been achieved regarding a proper follow-up policy for LS. Due to an increased risk for penile cancer, patients should at least be instructed regarding routine self-inspection.

▪ Hygiene

There is very little evidence establishing a link between penile hygiene and cancer. Nagpal et al.[45] showed that cancer of the uterine cervix is the most common malignancy in females in Punjab, India and postulated "that a common carcinogenic agent, either a virus or a biochemical (smegmatic) factor, may be responsible for the high incidence of carcinoma of the penis in males and carcinoma of the cervix in females". Van Howe and Hodges[46] investigated the carcinogenicity of smegma. After reviewing the available literature they stated: "Assertions that smegma is carcinogenic cannot be justified on scientific grounds."

One cross-sectional study[47] postulated an association between circumcision and penile hygiene. Poor genital hygiene behaviour was more common in uncircumcised (26%) than in circumcised men (4%). Of the circumcised men 37% washed more than once a day, compared with 19% of the uncircumcised.

Frisch et al.[48] investigated the long-term trends (Denmark 1943-90) in the incidence of penile cancer in an uncircumcised population. The authors concluded that the falling incidence of penile cancer in Denmark probably resulted from better penile hygiene due to improvement in sanitary installations in that country.

▪ PUVA treatment

The first description of a SCC after PUVA therapy for psoriasis was reported by Tam and coworkers[49] in 1979. In 1990 Stern[50] reported prospectively on 892 men in a 12-year follow-up period. In patients treated with high levels of oral methoxsalen (8-methoxypsoralen) and ultraviolet A photochemotherapy (PUVA) the incidence was 286 times that in the general population. There was a strong dose dependent increase in the risk of genital cancers. The same group reported further follow-up data in 2002. Although penile protection was administered during PUVA therapy, there was a persistent risk of genital tumors. PUVA patients should be advised to carefully shield the genitalia and observe skin changes, especially after high levels of PUVA therapy.

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SECTION II

Role of HPV vaccination and circumcision in the prevention of penile cancer

Penile cancer is a rare disease and optimal treatment should be delivered in specialist units by a multidisciplinary team. Based on the known aetiologies of penile cancer, a number of strategies for prevention emerge. In this section three robust scenarios are developed. These predict that by 2050 the incidence of penile cancer may increase or decrease by one fourth of the current incidence. All three scenarios indicate an increase in the number of elderly patients requiring treatment.

Multimodal therapy maximises outcomes in oncological, functional and psychological spheres. This is delivered by a team of specialists. Developing competencies to deliver optimal care requires several years of training. This section lays out the current and future issues likely to impact on the incidence of the disease and develops a number of scenarios to inform service planning.

Epidemiology

Squamous cell cancer (SCC) of penis is a disease with highly variable incidence globally. The incidence ranges from <0.5% of all male malignancies in the U.S. to 10%-20% in parts of South America, Asia and Africa.[1] The difference in incidence between countries appears to be explained by the variation in incidence of risk factors. In the UK there are approximately 300 new cases per annum. In a prospective study of 100 consecutive cases presenting to our unit, the average age at presentation was 62 with a quarter of cases occurring in men under 50 years of age.[2] The age at presentation is represented in Fig. 1.

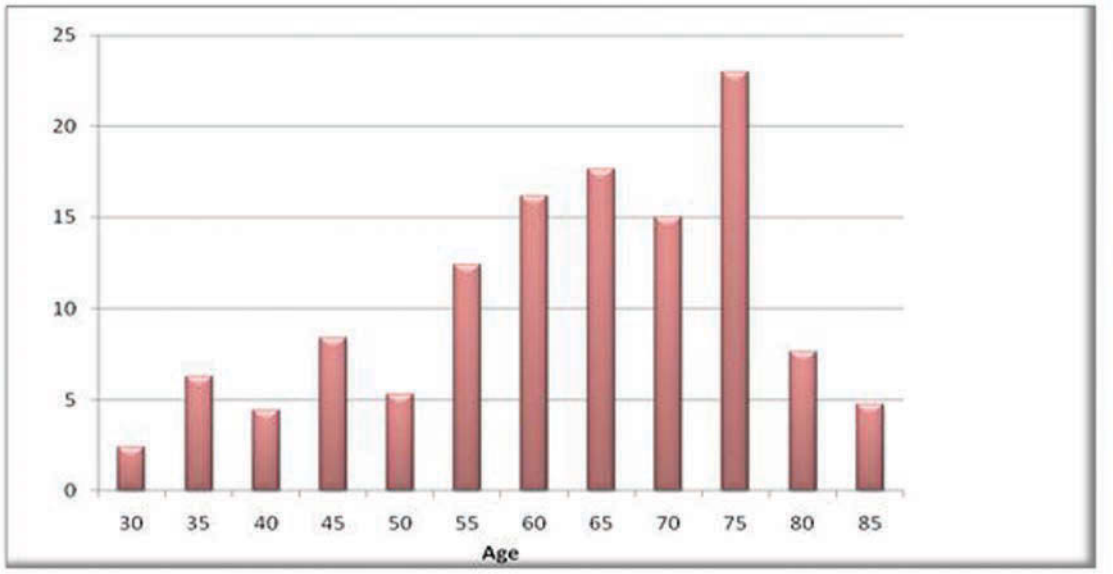

Fig. 1: *Age at diagnosis for a total of 100 consecutive patients (data from Hegarty, 2006[2]).*

Control of risk factors

The main risk factors for penile cancer are not being circumcised, infection with human papilloma virus (HPV), advancing age, poor hygiene and smoking. This chapter examines the effect of risk factor management and the likely impact on the patterns of incidence using a simple demographic model. Circumcision in childhood protects against this disease, probably by improving hygiene so that the penis is not chronically exposed to carcinogenic material. In 1855, Hutchinson proposed that circumcision could prevent infection with syphilis.[3] In a case-control study of 1913 couples, circumcised males had an OR for HPV infection of 0.37, when corrected for number of sexual partners and other potential confounding

factors. This was seen to reduce the risk of cervical cancer in the female partners of circumcised men.[4] HPV is associated with 90% of early stage cancer, but the presence of a foreskin probably facilitates the acquisition of the virus. Smoking also is a risk factor, probably through the contact of excreted chemicals in the urine trapped by a tight foreskin. These risk factors explain the low incidence of penile cancer in the US where neonatal circumcision rates are very high.

Scenario planning

Planning for the future is fraught with uncertainty. Forecasting involves predicting what will happen at a particular time. If this were possible then a strategy could be planned in advance to meet the challenge of predicted changes. However, in the absence of certainty, scenario planning examines a range of possible futures that may occur.

Rationale

Scenario planning is a means of linking multiple factors to generate a number of potential futures that can be used for strategic planning. It does not represent a forecast, as it provides a range of possible outcomes, or as defined by Porter[5] "an internally consistent view of what the future might turn out to be - not a forecast, but one possible future outcome". Scenario planning involves examining relevant parameters, either singly or in combination. This can lead to the formation of clusters of possible futures. These then inform the organization for strategic planning.

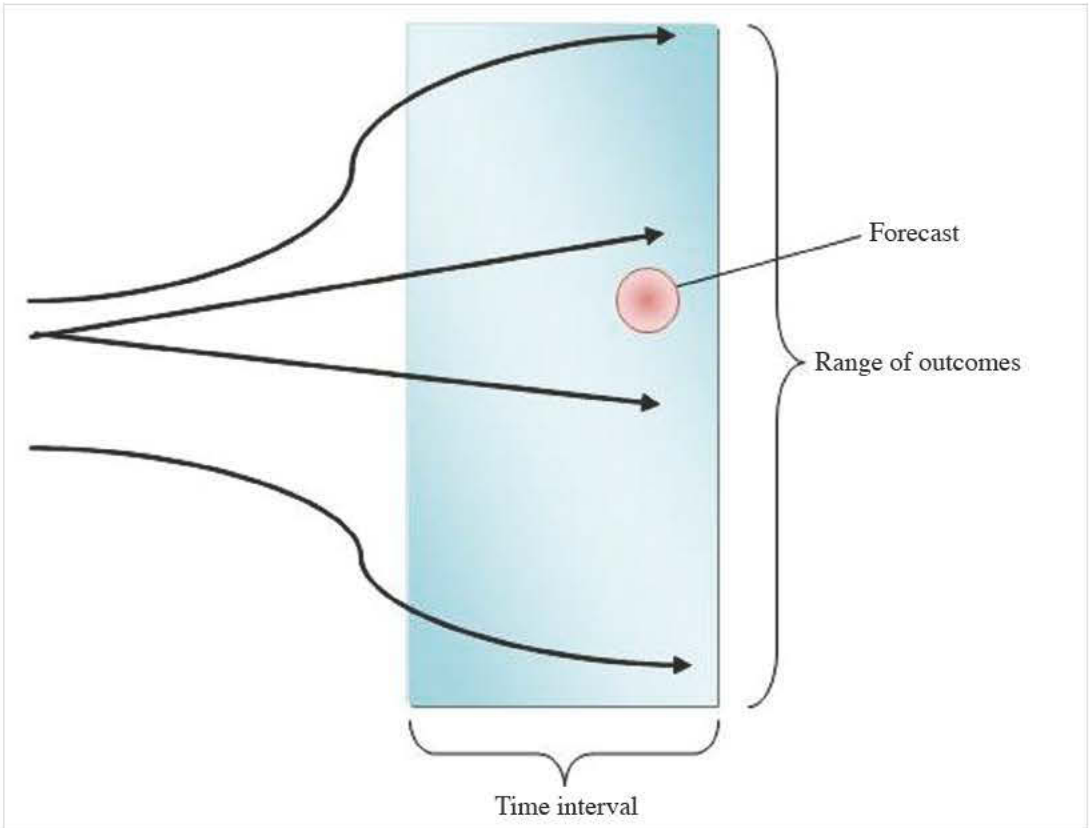

Fig. 2: *Where forecasting lies within a range of outcomes over time.*

Scenario planning and forecasting are illustrated in Fig. 2. Forecasting aims to give a precise outcome at a particular time point, whereas scenario planning provides a number of possible general scenes within a time-frame.

Grouping of issues

The main factors likely to influence the incidence of penile cancer are related to the three main risk factors for developing penile cancer, namely: age, HPV infection and being uncircumcised.

Age

The first scenario to consider is the projected natural history of change in incidence of the disease if nothing is done to prevent disease occurrence. A number of sources break down the population estimates according to 5-year age groups. The Office for National Statistics[6] in the UK demonstrates the proportion of people alive in each age group as a pyramid with males on the left and females on the right (Fig. 3).

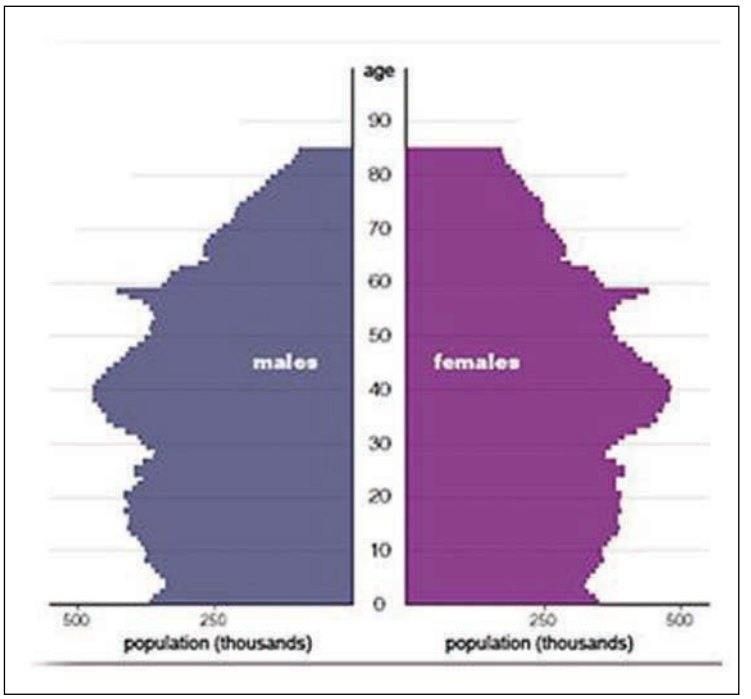

Fig. 3: *UK demographics according to gender from mid 2005 (Office for National Statistics, 2006).*[6]

In keeping with this pattern is another source of current and projected demographics from the Organisation for Economic Co-operation and Development (OECD).[7] Their data are based on birth rates, mortality and immigration. From these they derive the projected data for 2050 (Fig. 4).

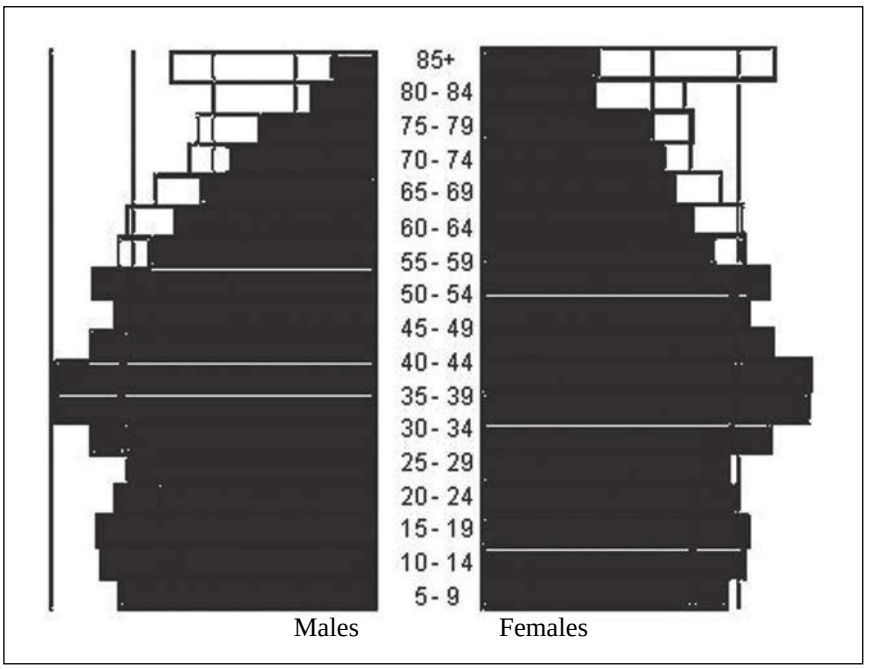

Fig. 4: *Population distribution among males and females in the UK. Blue bar represents 2000 data, whereas the other line in the bar represents projected demographics for 2050 (OECD Statistics Portal).*[7].

Despite differences between the sources and processing of data the age profiles for 2000 and 2050 are similar.[6] All OECD countries return similar trends regarding an increasing proportion of older males and females. These data allow the proportional change for each 5 year age group to be multiplied by our current data of men presenting with penile cancer as previously shown in Fig. 1. The transformation of these data is shown in Table 7 of the Appendix and represented graphically in Fig. 5.

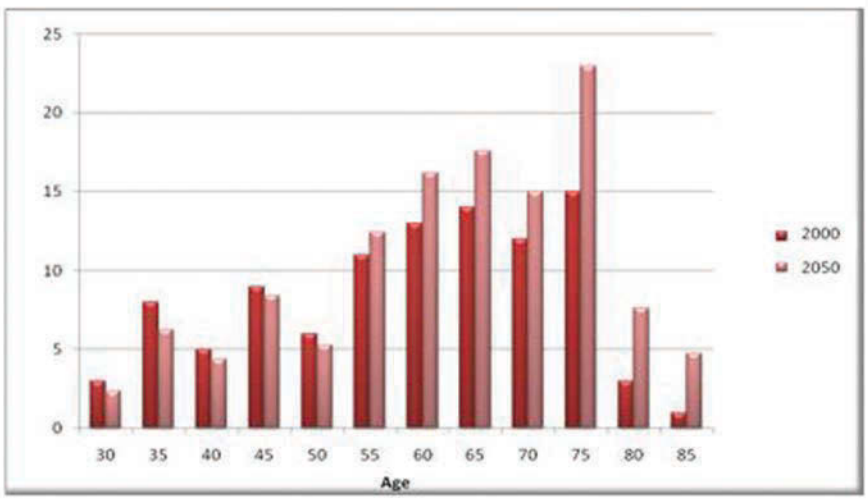

Fig. 5: *Projected increase in incidence by the year 2050.*

In the absence of preventative strategies, the relative increase in older men will result in an increase in incidence of approximately 23%. These transformed data are also used in the following two interventional scenarios.

Vaccine

The second scenario focuses on what effect a vaccine against HPV could have. In females the risk of cervical cancer is significantly reduced with the use of recently marketed vaccines.[8] The "me too" effect on penile cancer could be very relevant, as HPV is implicated in up to 90% of early penile cancer. Vaccinating males has been suggested to reduce the total HPV burden in the population as a whole.[9] This scenario goes to the extreme position of how much a national program of vaccinating all males aged up to 22 years, from the year 2007, would impact incidence of penile cancer in 2050. This assumes a well organized program that has full compliance due to a strong health promotion campaign. This scenario assumes a risk reduction of 90% for the cohort that receives the vaccine. The age of the men in 2050 will include those currently over age 22, who miss out on vaccination. This results in a drop in incidence to 73% of current rates as demonstrated in Fig. 6 (calculations in Appendix, Table 8), but with a greater proportion of patients in the older (unvaccinated) age groups.

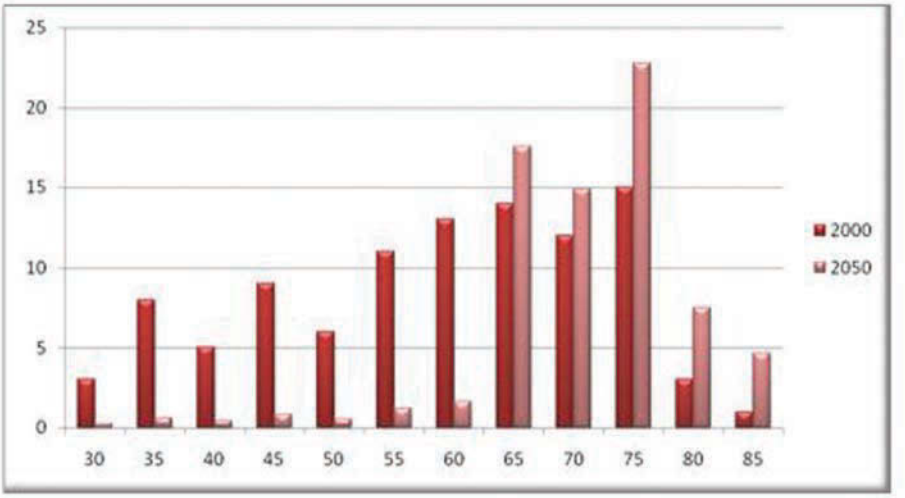

Fig. 6: *Incidence of penile cancer if vaccination program is successful.*

In this scenario, by 2050 only men over the age of 65 will have missed out on the vaccination program. Despite presuming that vaccination reduces the risk by 90%, the incidence by 2050 would only be reduced by 27%.

There is no evidence supporting the use of mass vaccination of the male population as a preventative measure in penile cancer (LE 4, GR D).

Circumcision

The final scenario is based on the resurgent interest in circumcision, due to the observed 50%-60% risk reduction of contracting HIV demonstrated in recent studies.[10,11] In the UK circumcision is performed for medical reasons in only 0.3% of boys under the age of five.[12] Circumcision reduces the risk of developing HPV to one third.[4] A putative program of circumcising all males up to the age of 12, presuming the maximal benefit of reducing the risk of penile cancer by two-thirds, translates into an increase of 5% in incidence by 2050 relative to current rates (Fig. 7, Table 9 in Appendix), with more patients in the older part of the range.

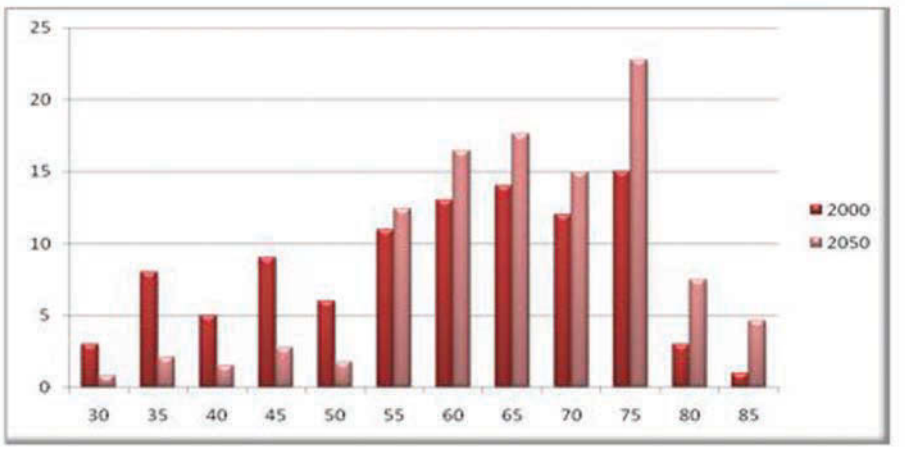

Fig. 7: *Incidence of penile cancer with program of circumcising boys under age 12.*

Despite such an enormous program there is surprisingly small change in total incidence due to the long lead-time to eventual effect combined with the changing age profile as in Figs. 3-5.

Limitation of scenarios

Scenario planning is limited by factors which include the quality of data on current and future trends, as well as the level of participation of stakeholders. Time-frames are also unclear with scenario planning as the rate and degree of change cannot be foretold with accuracy. However, scenarios do not serve as forecasts, rather they are formulated to guide decision-makers to consider a reasonable set of potential futures and plan accordingly.

Summary

This chapter has examined the chief factors likely to influence the number of cases of penile cancer for the year 2050. Three viable scenarios demonstrate that incidence will vary between 73% and 123% of current volume in the United Kingdom. In all scenarios the incidence is higher among older men.

Conclusion

The need for cancer services is likely to continue at levels similar to current demand. Patient demographics will alter, with older men in particular requiring treatment.

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APPENDIX

Table 7: Calculation of projected incidence of penile cancer for each 5-year age group in 2050 from OECD data. The relative change in each age group is calculated by dividing 2050 data by 2000 data. This factor is then multiplied by known current incidence of disease among 100 men, to yield projected incidence for 2050. This represents an increase of 23% in incidence of the disease.

Age	2000	2050	Ratio	Current	Projected
85+	1.1	5.1	4.6	1	4.6
80 - 84	1.6	4.0	2.5	3	7.5
75 - 79	2.9	4.4	1.5	15	22.8
70 - 74	3.7	4.6	1.2	12	14.9
65 - 69	4.3	5.4	1.3	14	17.6
60 - 64	4.9	6.2	1.3	13	16.4
55 - 59	5.6	6.3	1.1	11	12.4
50 - 54	7.0	6.1	0.9	6	5.2
45 - 49	6.5	6.0	0.9	9	8.3
40 - 44	7.0	6.2	0.9	5	4.4
35 - 39	7.9	6.2	0.8	8	6.3
30 - 34	7.9	6.3	0.8	3	2.4
Total	-	-	-	100	123

Table 8: Calculation of projected incidence of penile cancer for each 5-year age group in 2050 from OECD data, with risk reduction of cohort treated by vaccine aged 22 years old or less in 2007. This represents a decrease of 27% in incidence of the disease.

Age	2050	Risk Factor	Cohort Incidence
85+	4.6	1	4.6
80 - 84	7.5	1	7.5
75 - 79	22.8	1	22.8
70 - 74	14.9	1	14.9
65 - 69	17.6	1	17.6
60 - 64	16.4	0.1	1.6
55 - 59	12.4	0.1	1.2
50 - 54	5.2	0.1	0.5
45 - 49	8.3	0.1	0.8
40 - 44	4.4	0.1	0.4
35 - 39	6.3	0.1	0.6
30 - 34	2.4	0.1	0.2
Total	123		73

Table 9: Calculation of projected incidence of penile cancer for each 5-year age group in 2050 from OECD data, with risk reduction of cohort of boys treated by circumcision when under age 12 in 2007. This represents an increase of 23% in incidence of the disease.

Age	2050	Risk Factor	Cohort Incidence
85+	4.6	1	4.6
80 - 84	7.5	1	7.5
75 - 79	22.8	1	22.8
70 - 74	14.9	1	14.9
65 - 69	17.6	1	17.6
60 - 64	16.4	1	16.4
55 - 59	12.4	1	12.4
50 - 54	5.2	0.33	1.7
45 - 49	8.3	0.33	2.8
40 - 44	4.4	0.33	1.5
35 - 39	6.3	0.33	2.1
30 - 34	2.4	0.33	0.8
Total	123		105

SECTION III

Pathology of penile premalignant lesions

Introduction

SCC of the penis often develops in a pre-existing lesion (percutaneous growth). The lesions that are regarded as penile SCC premalignant lesions can be categorized as HPV related or due to chronic inflammation (Fig 8).

HPV related lesions include malignant giant condylamata acuminata, Bowenoid papulosis, Bowen's disease and erythroplasia of Queyrat (EQ), whereas those due to chronic inflammation include genital lichen sclerosus (LS) (balanitis xerotica obliterans - BXO), penile horn, leukoplakia and pseudoepitheliomatous, keratotic and micaceous balanitis (PKMB).

HPV related pre-cancerous lesions are associated with persistent HPV type 16 and 18 infection. Giant condyloma is associated with HPV 6 and 11.[1] In a large multicenter study of HPV DNA prevalence in penile cancer, HPV DNA was detected in 100% of condylomas, 90% cases of dysplasia, and 42% of penile carcinomas. However there were significant differences in HPV prevalence among the different histological tumor subtypes. Keratinizing and verrucous carcinoma were positive for HPV DNA in 34.9% and 33.3% of the cases, respectively. Basaloid and warty penile cancers were positive for HPV DNA in 80% and 100% of the cases, respectively. The difference in HPV prevalence between these two groups was statistically significant. The results suggest that penile intraepithelial neoplasia or penile dysplasia, as defined currently, is a precursor lesion to only a subset of tumors, which include basaloid and warty carcinomas (LE 3).[2] Verrucous and keratinizing SCC could be a result of the chronic inflammatory processes.

It is essential to clinically and pathologically differentiate pre-cancerous lesions that are related to HPV from benign ones. It is also vital to be aware that pre-cancerous HPV related lesions can co-exist with benign ones.

HPV related penile premalignant conditions

- **Giant condyloma (Buschke-Löwenstein tumor)**

Other names for this tumor include giant malignant condyloma, verrucous carcinoma and carcinoma-like condyloma. However, it is now believed that giant condyloma is different from verrucous carcinoma.[3] This stems from the finding that papillary and verrucous variants of SCC are not HPV related, whereas the basaloid warty variants and giant condyloma are. In one series, 117 formalin-fixed specimens of penile cancer were PCR analyzed for HPV DNA and the findings revealed no significant association with typical keratinizing verrucous SCC of the penis, whereas the association with basaloid SCC was 75%.[4]

- **Clinical features**

The disease usually affects the uncircumcised of any age from 18 years to 86 years. The patients notice a slow growing cauliflower lesion that may reach more than 5 cm in the preputial sac. The disease can affect other anogenital structures like the groin, urethra and the anal canal. They may develop fistulae of the urethra and rectum and ulceration of the underlying subcutaneous tissues as a result of down-growth of the disease into the underlying structures. Infection is a usual feature in this condition.[5] On the penis this destruction can lead to damage of the glans penis and this may mimic aggressive basaloid carcinoma.[4]

- **Histology**

The histology is mixed with benign condyloma with areas of atypical cells or well differentiated squamous cell CIS. There are reports of tumors as a mixture of benign condyloma, warty carcinoma and either basaloid or atypical SCC.[6]

- **Progression to invasive squamous cell carcinoma (SCC)**

Foci of infiltrating carcinoma may be found in 23% of cases and there are reports of progression to carcinoma.[6-9] Due to the clinical similarity of some varieties of giant condyloma and benign condyloma, basaloid SCC and co–existence of giant condyloma and infiltrative carcinoma, biopsy is necessary whenever this lesion is suspected (LE 3).

Bowenoid papulosis

- **Clinical features**

This usually affects men below the age of 28 years, especially among the sexually promiscuous, but it also occurs in men above 50 years. The patients may notice a lesion on the penis that could itch periodically, give a burning sensation, and occasionally give localized dyspareunia with recurrent balanoposthitis.[10,11] When examined, these are usually multiple maculopapular lesions with a smooth velvety surface. The lesion could at times be single or may coalesce into large plaques. It is rare that the lesions are erosive. The colour depends on the pigmentation of the location of the lesion: those involving the inner prepuce are usually brownish, salmon red or grayish white and leukoplakia-like. Lesions that affect the more pigmented area of the penile shaft tend to be ash gray or brownish black.[12] Differential diagnosis includes flat condylomas, lichen planus and psoriasis.

- **Histology**

It has histopathological features of Bowen's disease.[13]

- **Progression to malignancy**

It usually runs a benign course with possible spontaneous regression. It may rarely evolve toward an invasive cancer, especially in immune suppressed individuals (LE 3).[14-16]

Bowen's disease and erythroplasia of Queyrat

In one study 12 paraffin-embedded biopsies from 8 patients with penile erythroplasia of Queyrat and control biopsies of genital Bowen's disease and of premalignant/malignant cervical or vulvar lesions were analysed. All erythroplasia of Queyrat patients were positive for HPV DNA, but none of the controls.[17]

Bowen's disease and erythroplasia of Queyrat are the same disease with different clinical presentation. If it is on the penile shaft the name Bowen's disease is used, and when it involves the inner aspect of the prepuce or the glans penis it is called erythroplasia of Queyrat. Both diseases are HPV 16 and 18 related, with HPV type 16 being more common (80%). Bowen's disease and erythroplasia of Queyrat are both histologically carcinoma in situ (CIS).

Bowen's disease (squamous cell carcinoma in situ)

- **Clinical features**

Patients are commonly elderly. The patient complains of a lesion on the shaft of the penis which may be a single scaly sharply defined erythematous plaque. Other areas like the inguinal or suprapubic area could be involved. Sometimes the lesion is more than one. Lesions may sometimes be heavily pigmented, resembling melanoma.[18] The lesions could appear in the following different forms: crusted and ulcerated plaques, keratotic plaques and elevated flesh-coloured plaques. Differential diagnosis includes Bowenoid papulosis, psoriasis and superficial basal cell carcinoma. Biopsy is required to confirm the diagnosis.

- **Transformation to malignancy**

Invasive SCC may arise in 5% of long-standing cases.[19]

Erythroplasia of Queyrat

This is carcinoma in situ (CIS) histologically.[20] It is a rare condition that affects men of average age 61 years.[21] Most of the time there are no symptoms, but patients may complain of a lesion that is painful, may bleed, and have inability to retract the prepuce due to crusting and scaling. The majority (about 80% to 90%) are uncircumcised.[22] On examination there could be single or multiple lesions with a slightly raised, erythematous, sharply defined plaque on the glans penis or inner prepuce. The texture is smooth, velvet, scaly or verrucous. This may co-exist with non-tender polymorphic warty lesions. It may be eroded and ooze occasionally.[22,23] The lesions may appear on other sites like the groin and scrotum.[24] The differential diagnosis includes eczema and psoriasis.[18]

- **Transformation into malignancy**

About 10%-30% of erythroplasia of Queyrat is reported to transform into SCC.[25,26] Poor hygiene, lack of circumcision, chronic irritation, immunosuppression, HPV genomic alterations, and coexistence of other viral or inflammatory penile diseases (LS, PKMB, lichen planus) are implicated in the pathogenesis of this condition.

Pseudoepitheliomatous, keratotic and micaceous balanitis (PKMB)

PKMB is a rare condition of unknown etiology affecting elderly men.[27] Patients complain of inability to retract the prepuce. On examination the lesion appears as a single, well demarcated, elevated growth on the glans penis. The surface may be scaly, from which a thin folia can be peeled and that could form a keratotic horny mass. It usually occurs on the glans of older uncircumcised men. Clinically the skin is hyperkeratotic and inelastic. Histologically it has hyperkeratosis with prominent rete ridges and a dense dermal polymorphonuclear infiltrate and pseudo-epitheliomatous hyperplasia.[26,28] This picture transforms into low grade SCC within a few years.[29,30] All reported cases have transformed into malignancy (LE 3).

Leukoplakia

This occasionally occurs on the glans or prepuce as a whitish and slightly infiltrated verrucous plaque. The histology is that of hyperkeratosis, parakeratosis and irregular acanthosis or atrophy of the malpighian layer, with altered keratinocyte arrangement and possible cellular atypia. There are reports of transformation into malignancy, and ulceration, erosion, or fissuring is usually a sign of malignancy.[20,15]

Penile horn

It is a rare form of cutaneous horn of unknown etiology.[24] It occasionally occurs on the glans as a hard and conical keratotic mass with a bulging erythematous base. The histology is that of benign epidermoid outgrowth or various epithelial disor-

ders with warts, keratoacanthoma, intraepithelial carcinoma, SCC or verrucous carcinoma.[29,31]

Histologically it appears like a wart with excessive keratosis, acanthosis, dyskeratosis, papillomatosis and chronic inflammatory infiltration in the adjacent dermis. Approximately 30% of penile horns transform into SCC, the majority of which are low grade (LE 3).[32]

Balanitis xerotica obliterans (BXO) or lichen sclerosus (LS)

This is a chronic inflammatory skin condition of unknown cause. It occurs on the glans and prepuce with a mean age of 60 years (Fig. 9).[33] Histologically there is hyperkeratosis of the epithelium with atrophic thinning of the rete pegs, sometimes with cleft formation, a band-like infiltrate of lymphocytes and plasma cells in the dermis. Vacuolar degeneration of the basal layer may be present. The papillary and reticular dermis present a "washed out" appearance and dermal collagen forms a homogenous band at the dermal-epithelial junction in conjunction with elastin fibres, to produce an amorphous hybrid substance and hyalinization of collagen in the upper dermis.[34]

▪ Malignant transformation

There is a well documented association between vulvar LS and SCC.[35] The pre-cancerous nature of BXO (or LS) of the penis is not as well studied as in the vulva, but the close association with penile carcinoma at least suggests a common aetiology (Figs. 10, 11).[20] Published reports that link penile cancer to BXO as a cause include case reports.[36-38] Two case series reported an incidence of 2.6%–5.8% of penile carcinomas in patients with BXO.[38,39] In a study of 155 patients with penile malignancy BXO was an associated finding in 28% of the patients. In this study, only patients with histologically confirmed BXO were included in the study.[20] Powell et al. reported an incidence of 50%.[40] Barbagli et al.[41] retrospectively reviewed the histology and clinical records of 130 patients with LS involving the male genitalia and reported premalignant or malignant histopathological features in 11 (8.4%), including SCC in 7 (64%), verrucous carcinoma in 2 (18%), erythroplasia of Queyrat in 1 (9%) and SCC associated with verrucous carcinoma in 1 (9%). In 6 of 11 patients (55%) the histological study showed the presence of epithelial dysplasia (LE 3).

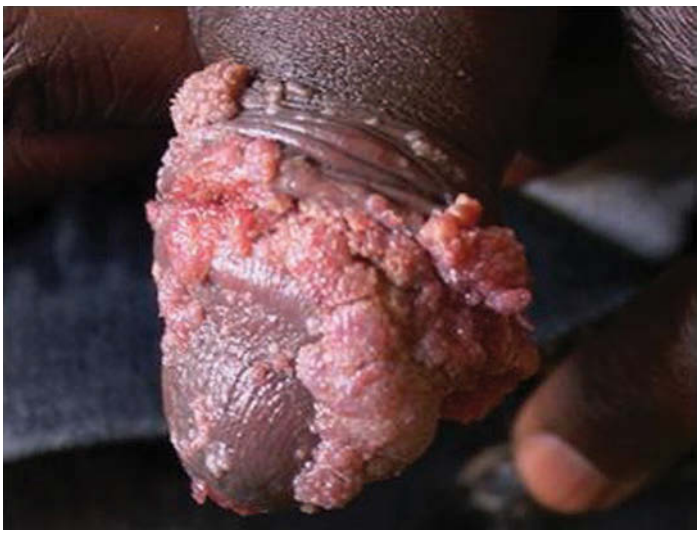

Fig. 8: *Benign condyloma.*

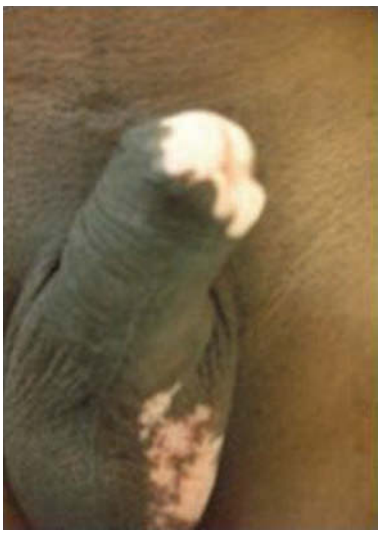

Fig. 9: *Balanitis xerotica obliterans .*

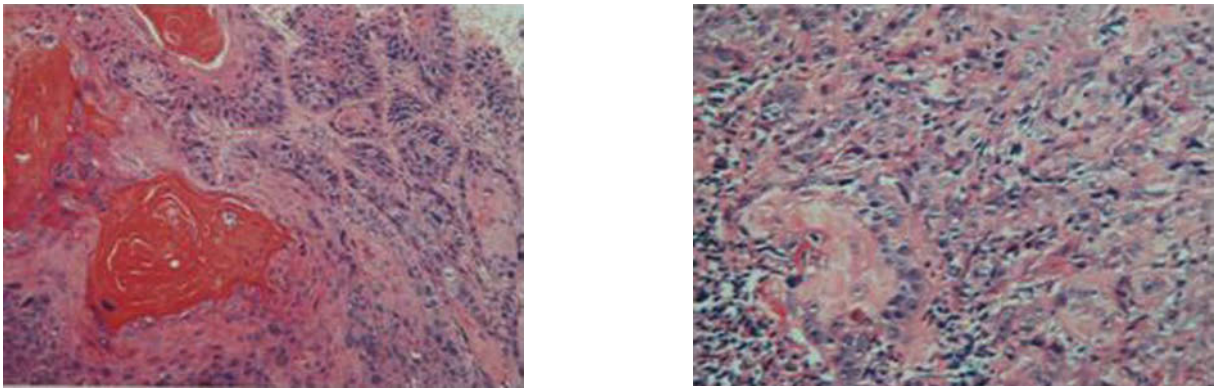

Fig. 10: *Sections of (A) the glans penis and (B) prepuce show similar findings of an invasive squamous cell carcinoma. The surface of the tumour has papillary appearance associated with koilocytic atypia consistent with a background condyloma acuminatum (A). The deep portion shows infiltrating nests of neoplastic squamous cells with foci of keratinization (B).*

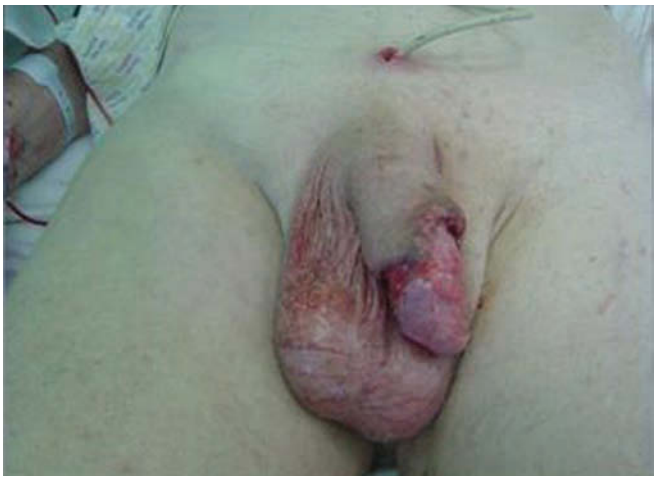

Fig. 11: *Squamous cell carcinoma arising in condyloma acuminatum associated with squamous cell carcinoma in situ.*

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SECTION IV

Treatment of penile premalignant lesions

Introduction

A number of pre-malignant lesions of the penis have been described. An assumption is made that all such lesions have the potential to develop into invasive carcinoma and thus treatment should be directed towards complete oncological clearance. Because of the low prevalence of penile cancer and small numbers of studies, the natural history of many of these lesions is largely unknown, although biologically they appear to be all considered as potentially invasive tumors, with differing degrees of invasive potential. The histopathology of such lesions has already been documented in the previous section. In this section, premalignant lesions have been divided into those which represent true CIS histopathologically (e.g. Bowen's disease of the penis, erythroplasia of Queyrat) and those pathological entities which include penile horn and giant condylomata, which have a documented association with penile carcinoma.

The aetiopathogenesis and association of BXO with SCC of the penis is largely unknown (see Section III). The evidence base for the association of BXO and carcinoma is not robust[1] and therefore in the context of cancer induction and treatment there are no current recommendations that can be made in terms of long-term follow-up or treatment of patients diagnosed with this condition. In order to identify patients who may be at risk of developing carcinoma long-term prospective studies are needed with the appropriate control.

The following lesions have been shown to have invasive potential or are associated with penile squamous cell carcinoma:

- Bowenoid papulosis
- Erythroplasia of Queyrat
- Bowen's disease of the penis
- Genital lichen sclerosus (LS) (balanitis xerotica obliterans)
- Penile horn
- Leukoplakia
- Pseudoepitheliomatous, keratotic and micaceous balanitis (PKMB)
- Malignant giant condylomata acuminata

Carcinoma in situ of the penis

In this section, CIS of the penis refers to erythroplasia of Queyrat, Bowen's disease and Bowenoid papulosis.

A number of surgical and medical therapies have been advocated as treatment modalities for CIS of the penis:

- topical 5-fluorouracil
- topical imiquimod
- topical interferon alpha-2a
- cryosurgery
- laser therapy (photodynamic therapy)
- surgical excision with skin grafting (glans resurfacing).

Staging of the primary lesion

It is mandatory to stage the primary lesion histologically. Multiple and deep biopsies should be included in the specimen, because often there may be foci of invasive elements. A gadolinium enhanced MRI scan after the induction of an artificial erection with PGE1 may be of use in staging these lesions to exclude invasive components (Fig. 12).[2]

Topical agents

Topical 5-fluorouracil (5-FU) is a structural analogue of thymine which blocks DNA synthesis by inhibiting thymidylate synthetase. Topical 5-flourouracil has been used as a cream for the treatment of CIS of the glans penis (erythroplasia of Queyrat) and cellular atypia.[3,4] In one such study[3] seven men with histopathological confirmation of erythroplasia of Queyrat were cured of malignancy following application of 5-FU. The men remained recurrence-free for up to 70 months. Several other studies have confirmed the clinical efficacy of 5-FU in the treatment of erythroplasia of Queyrat. 5-Fluorouracil has also been used in treatment of Bowen's disease of the shaft of the penis.[5]

Imiquimod is an imidazoquinonin tetracyclic amine and exhibits both anti-viral and anti-tumor properties. The immune response modification may at least partly be dependent on its ability to induce the production of interferon alpha. Imiquimod has been used in the treatment of a number of pre-malignant lesions including erythroplasia of Queyrat.[6-9]

Laser therapy has been used in the treatment of both pre-malignant and malignant squamous cell lesions of the penis. In one such study,[10] 19 patients with penile intraepithelial neoplasia and CIS were treated with either CO_2 or Neodymium YAG laser therapy. One patient had treatment with a KTP laser. Follow-up after two years showed that the patients remained free from malignancy. In a further study by Tietjen and Malek[11] 92 patients were treated with laser therapy. The authors reported excellent cosmetic results and preservation of sexual function, although long-term surveillance of patients is not available.

In other studies[12-14] photodynamic therapy has been used in the treatment of both Bowen's disease of the penis and erythroplasia of Queyrat. Axcrona et al.[12] treated a group of 10 patients with cellular atypia/CIS with photodynamic therapy. The group consisted of 5 patients with primary lesions and 5 with cellular atypia after organ-preserving surgery for carcinoma of the penis. After a median follow-up period of 20 months 3 of the 10 patients had histopathological residual disease. The authors concluded that photodynamic therapy for CIS appears to achieve oncological control with organ preservation. Similarly Stables et al.[14] reported the use of topical ALA and photodynamic therapy to treat pre-malignant and malignant skin diseases. The authors presented 4 patients with erythroplasia of Queyrat treated with topical ALA photodynamic therapy. Of 2 patients with limited disease, one achieved long-term complete response whilst another had complete response for 18 months. The patients with more extensive disease saw an improvement. Neodymium YAG laser[15] has been used in the treatment of Bowenoid papulosis of the penis.

Sonnex et al.[16] have described the treatment of erythroplasia of Queyrat with liquid nitrogen cryosurgery in 2 cases. Equally, SCC of the penis has been treated with cryosurgery, as has the Buschke-Löwenstein lesion.

In a study by Van Bezooijen et al.[17] 18 patients with CIS of the penis were treated with Neodymium YAG or carbon-dioxide laser. No complications developed and cosmetic outcome was excellent. Of the 3 patients who received repeat treatment there was disappearance of the lesion. At an average follow-up of 25 months CIS occurred in 5 patients, and one developed infiltrating carcinoma.

Laser therapy appears to be an oncologically safe treatment for CIS of the penis, although there is a high incidence of recurrence, which suggests that vigilant follow-up is required.

Surgical excision (excluding laser excision) has been used in the treatment of CIS. Two studies have reported on the role of resurfacing and glanular reconstruction using split thickness skin grafting.[18,19] In one such study[19] patients underwent total glans resurfacing involving removal of the skin of the glans penis down to its spongiosum. Six patients had recurrent erythroplasia of Queyrat after 5-FU therapy whilst one patient had a severe allergic reaction to 5-FU and one patient had no response to 5-FU or imiquimod. Two patients had extended glans hyperkeratosis and severe dysplasia. There were no postoperative complications and in all cases pathological resection margins were clear. At median follow-up of 30 months there was no evidence of recurrent disease. The authors suggested that surgical excision with skin grafting may minimise the local recurrence rate by replacing diseased epithelium with healthy skin.

Treatment of other pathological premalignant conditions

This group of conditions includes penile lesions which may not histopathologically contain malignant cells, although they have a potential to develop such cells or invasive elements. The terminology to describe such lesions is unclear, as some of these lesions will have no histopathological features of malignancy and after removal follow an entirely benign course. In contrast, some such lesions, e.g. giant condylomata, may have invasive elements, although clinically they may not differ from a benign lesion.

The following cutaneous conditions have been described as having malignant potential or a close association with SCC of the penis and are thus described as premalignant.

In diagnosing such conditions, representative biopsies of the lesion should be obtained to exclude the presence of malignancy, while strict follow-up is advised in view of the association with penile SCC.

Penile cutaneous horn

Cutaneous horn of the penis has a propensity to transform into malignancy in about 30% of cases. The number of cases described in the literature is small and thus recommendations for treatment are not clear. Cruz-Guerra et al.[20] have reported a case of malignant recurrence of a cutaneous horn of the glans penis. The biopsy of the lesion was reported as hyperkeratosis with pseudoepitheliomatous hyperplasia. Partial penectomy of the glans penis was performed after recurrence three months later and SCC was found in the base of the lesion. The authors emphasized the capacity of penile cutaneous horn to become malignant and recommended close observation of these lesions after excision. Similarly, Fields et al.[21] reported a case of a patient treated with surgical excision and external radiation due to invasive components of the lesion.

Buschke-Löwenstein tumor

The histology of this lesion is mixed with benign condyloma, with areas of atypical cells or well differentiated SCC in situ.

Foci of infiltrating carcinoma may be found in 23% of cases and there are reports of progression to SCC as already mentioned. The lesions can be locally destructive. Gilbert and Beckert[22] reported circumcision and Neodymium-YAG laser as treatment for giant condylomata acuminata of the penis. Two cycles of interferon therapy were also administered postoperatively. The authors concluded that this therapy provides excellent cosmetic and functional results.

Others have reported combination treatment with 5-fluorouracil cream and electrocautery combined with surgical excision as treatment modalities for this condition.[23] Hatzichristou et al.[24] have reported outcome in patients with exophytic, papillary lesions involving the glans penis and advocate glansectomy as the treatment of choice in patients with Buschke-Löwenstein tumors of the penis. Biopsy led to the diagnosis of verrucous carcinoma in 4 patients and giant condyloma acuminatum in 3 patients. A glansectomy was performed in all of the patients. At 18 to 65 months of follow-up all patients were disease free, with one patient requiring further treatment because of local recurrence of the tumor.

Summary

Several treatment modalities have been used in the management of pre-malignant lesions of the penis (Table 10). However, evaluation of these studies is limited due to the small number of patients and the varied treatment regimens that have been used.

Overall, based on the evidence in the literature, the following modalities have been shown to be effective in the treatment of the following pre-malignant conditions:

Table 10: Penile lesion	Treatment modality
Erythroplasia of Queyrat	Imiquimod, 5-FU, cryosurgery, laser, photodynamic therapy, surgical excision
Bowen's disease of the penis	Imiquimod, 5-FU, cryosurgery, laser, photodynamic therapy, surgical excision
Bowenoid papulosis	Laser, imiquimod
Penile horn	Surgical excision
Malignant giant condylomata acuminata	Surgical excision, 5- FU, immunotherapy
Leukoplakia	Bleomycin

Future research should be targeted at further evaluating the various treatment modalities in the treatment of CIS. This will require multi-institutional collaboration as the numbers of patients seen by single institutions are small. In order to accumulate the appropriate number of patients, multi-institutional studies are recommended.

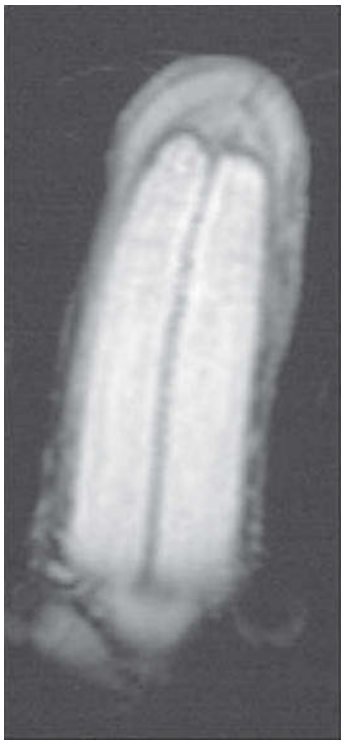

Fig. 12: *A gadolinium enhanced MRI of the penis following the administration of intra-cavernosal PGE1.*

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Summary of the levels of evidence

1. Circumcision in early childhood may help prevent penile cancer by eliminating phimosis and preventing cofactors such as HPV infection and improving hygiene (LE 3). With such small numbers of patients with penile cancer (for example in Europe and the USA) it would be difficult to justify routine circumcision in all boys. A program of circumcising all males up to the age of 12, presuming the maximal benefit of reducing the risk of penile cancer by two-thirds, translates into an increase of 5% in incidence by 2050 relative to current figures due to the aging population, and is therefore difficult to justify.
2. Smoking has been repeatedly shown to have a consistent association with penile cancer. Smokers have a considerably increased risk for invasive cancer compared to non-smokers. It is therefore recommended that smoking cessation should be strongly advocated through educational programmes (LE 3).
3. The role of HPV infection in the induction of penile carcinoma appears to be variable and is not clear, although there does appear to be an association with some subtypes of HPV. The influence of HPV DNA expression on the prognosis of penile cancer is also not clear (LE 3).
4. Long-term data are currently not available that male vaccination could prevent HPV associated penile cancer development (LE 4). At present one can only assume that male vaccination could prevent HPV associated penile cancer development and it is possible that targeting high risk groups may reduce the risk of developing HPV associated penile cancer. Despite presuming the best scenario that vaccination reduces the risk by 90%, the incidence by 2050 would only be reduced by 27%. However, a more plausible strategy may be that of avoiding transmission of HPV infection between sexual partners by condom usage.
5. The pathological nomenclature describing the various penile premalignant lesions is confusing and not consistently described in the literature (LE 3). This would require a consensus opinion from a pathology steering committee.
6. True carcinoma in situ of the penis should be distinguished from those conditions which are associated with penile cancer, as the natural history and treatment of the two pathological entities differ considerably (LE 3).
7. The pre-cancerous nature of balanitis xerotica obliterans (BXO) or lichen sclerosus (LS) of the penis is not well established, although there does appear to be an association (LE 3). The level of evidence suggesting a link between the two conditions is weak, without the appropriate control populations. Based on the available data in the literature, routine life-long follow-up of all men with BXO cannot be justified, but self-examination can be advocated (LE 4).

Recommendations for penile cancer – prevention and premalignant conditions

- A program of circumcising all males up to age of 12 to prevent penile cancer is difficult to justify (GR D).
- Smoking cessation should be strongly advocated through educational programmes (GR C).
- Male vaccination to prevent HPV associated penile cancer development can not be recommended on the currently available data (GR D).
- The pathological nomenclature describing the various penile premalignant lesions is confusing and not consistently described in the literature, thus a pathology steering committee should be established (GR B).
- The pre-cancerous nature of balanitis xerotica obliterans (BXO) or lichen sclerosus (LS) of the penis is not well established, thus routine life-long follow up of all men with BXO cannot be currently justified (GR C).
- Multinational prospective trials are needed to define the best management of pre-malignant lesions of the penis (GR C).

Committee 4

Diagnosis and Staging of Penile Cancer

Chair:

Arturo Mendoza-Valdés (Mexico)

Members:

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Antonio Pompeo (Brazil)

CONTENTS

Diagnosis and Staging of Penile Cancer

Diagnosis and Staging of Penile Cancer

A. Mendoza-Valdés, C.F. Heyns, A.C.L. Pompeo

Diagnosis

In order to diagnose penile carcinoma, the first step is careful examination of the primary lesion, followed by histological confirmation and thorough physical examination of the patient, looking for regional lymph nodes and distant metastases. Early diagnosis of penile cancer is extremely important, because delayed diagnosis is associated with increased mortality.[1] A high index of suspicion is essential, and all penile lesions that do not respond to a short trial of therapy should undergo biopsy for histological evaluation.[2,3]

Survival is related to stage, and accurate staging is essential to maximize survival.[4] However, there is considerable discrepancy between clinical and pathological staging of the primary penile lesion as well as the inguinal lymph nodes, because of concomitant inflammatory changes and difficulties in defining the relevant anatomical structures.[2]

Local tumor staging

Regarding examination of the primary lesion the characteristics that should be recorded are the:

- diameter of the penile lesion(s) or suspicious area(s)
- site(s) on the penis involved (e.g. foreskin, glans, shaft)
- number of lesions
- color and morphology, i.e. whether flat, papillary, nodular, ulcerating or fungating
- relationship with other structures (e.g. submucosa, corpus spongiosum, corpora cavernosa, urethra)
- boundaries of the lesion.

In a study of 118 patients with squamous cell carcinoma (SCC) of the penis Horenblas et al. analyzed the accuracy of staging. The primary tumor (T-category) was classified incorrectly in 26% of the cases. Overstaging was noted in 10% because of unsuspected infiltration, and overstaging was noted in 16% because of edema and infection masking the actual size and giving a misconception of infiltration, and also because of primary presentation as large exophytic tumors with no or minimal histopathological infiltration (LE 3).[5]

Imaging techniques may be useful for staging and planning therapy.[6] Although ultrasound (US) or magnetic resonance imaging (MRI) are recommended in combination with clinical examination to help delineate corpora cavernosa infiltration, experience with US has indicated that this technique is unreliable, especially with regard to microscopic invasion of the glans.[7,8]

Horenblas et al. performed US assessment with a 7.5 MHz linear array small parts transducer in 17 patients with penile cancer. All tumors were identified as hypoechoic lesions. US examination in the region of the glans could not differentiate between invasion of the subepithelial tissue and invasion into the corpus spongiosum, but absence or presence of invasion into the tunica albuginea of the corpus cavernosum was clearly demonstrated. Accurate measurement by US of maximum tumor thickness was seen in 7/16 examinations. The authors concluded that while US examination is inexpensive and easily done, it is not accurate enough for staging small penile cancers located at the glans. However, for larger tumors US can be a useful addition to physical examination by delineating reliably the anatomic relations of the tumor to structures such as the tunica albuginea, corpus cavernosum and urethra (LE 3).[7]

Agrawal et al.[9] performed US using a 7.5-MHz linear-array transducer in 59 patients with penile

carcinoma. The US measurement of tumor extent was compared with clinical and pathologic measurements. The overall mean difference in the tumor extent between clinical and gross pathologic evaluation was 3.9 mm (range, 1-9 mm), whereas the overall mean difference between US and gross pathologic evaluation was 1.2 mm (range, 1-7 mm). Lesions involving the glans alone were more often underestimated by clinical examination than were lesions involving the shaft. The error in measuring the extent of tumor by US was not related to the site of the lesion. The tumor was hyperechoic in 21 cases (36%), hypoechoic in 28 cases (47%), and of mixed echogenicity in 10 cases (17%). There was no significant association between echogenicity and tumor morphology or grade. The authors concluded that US gives a more accurate estimate of penile tumor extent than does physical examination (LE 3).[9]

In a study of 33 patients with penile carcinoma Lont et al.[10] compared the accuracy of physical examination, US and MRI with histopathological examination of the penectomy specimen. Tumor size was determined with the highest precision by physical examination, while US and MRI were less precise. In assessing infiltration depth, US and MRI had comparable precision. The positive predictive value (PPV) of corpus cavernosum infiltration was 6/6 for physical examination, 4/6 for US and 6/8 for MRI; the sensitivity was 6/7, 4/7 and 6/6, respectively. The authors concluded that physical examination is a reliable method for estimating penile tumor size and determining corpus cavernosum infiltration, while tumors for which infiltration of the corpora can not be determined properly by physical palpation only should be examined by imaging (LE 3).[10]

There are few studies in the literature reporting the use of MRI in staging penile neoplasms and they are limited by small patient numbers.[10-15] A study of 9 patients with penile cancer compared staging by clinical examination, MRI with gadolinium contrast enhancement, and surgery. T1-weighted sequences did not clearly demonstrate the margins of the tumor. T2-weighted sequences were the more useful in 5 patients, whereas contrast-enhanced T1-weighted sequences allowed better delineation of the lesion in only 3 patients. Clinical examination correctly staged 6/9 tumors, MRI 7/9 tumors and the combination of both examinations 8/9 tumors (LE 3).[13]

Scardino et al. compared local clinical examination, MRI with artificial erection, and pathologic staging in 9 cases of penile cancer.[15] Erection was obtained by injecting 10 microgram prostaglandin E1 into the corpora cavernosa. T1- and T2-weighted MRI with and without contrast was obtained using a phased array coil. The MRI and pathologic staging coincided in 8/9 patients. One patient developed priapism after prostaglandin injection, which was relieved by aspiration of the corpora cavernosa.[15] Primary penile cancers are most often solitary, ill-defined infiltrating tumors that are hypo-intense relative to the corpora on both T1- and T2-weighted images. The tumors enhance on gadolinium-contrasted images, although to a lesser extent than the corpora cavernosa (LE 3).[16,17]

In a study of 55 men with invasive penile carcinoma, MRI with artificial erection was compared against final histopathologic stage. Stage-specific sensitivities and specificities were: T1 (85%; 83%), T2 (75%; 89%) and T3 (88%; 98%). MRI accurately predicted corpora cavernosa invasion (positive predictive value (PPV): 100%; negative predictive value (NPV): 100%) (LE 3).[18] The authors noted that 10 cases (18%) were inaccurately staged by the radiologists, but these errors did not impact on clinical decision making. The errors seemed to arise because of technical problems including lack of erection, motion artefact, previous radiotherapy to the penis, and associated infection. The authors suggested that in the presence of one or more of these factors, it is prudent to rely more strongly on intraoperative frozen section (LE 3).[18]

In a study of 13 patients with penile cancer, local staging by clinical examination was compared with MRI combined with pharmacologically induced penile erection (PIPE) using 10 microgram prostaglandin E1. MRI-PIPE correctly staged 12/13 patients, failing to detect one in situ carcinoma. Clinical examination correctly staged 8/13 patients, over-staging 2 patients and under-staging 3. MRI-PIPE performed better than clinical

examination and changed treatment planning in 3 patients (LE 3).[19].

When used in conjunction with artificial erection, MRI highlights the boundaries between corpus spongiosum and corpora cavernosa (high signal) from the tunica albuginea (low signal) seen as a black line on T2-weighted images.[18] It has been suggested that MRI is the most accurate imaging modality in the assessment of primary penile cancers, which usually manifest as solitary, ill-defined infiltrating tumors that are hypointense on both T1- and T2-weighted MR images. T2-weighted MR imaging allows delineation of the tumor margin and its extension into the penile shaft. On gadolinium-enhanced T1-weighted images, the tumors enhance to a greater extent than do the corpora cavernosa (LE 3).[17] MRI also offers the advantage of imaging in three orthogonal planes, giving more anatomic detail of the primary tumor.[20]

Computed tomography (CT) does not clearly depict the local extension of primary penile cancer; however, it is useful in assessing metastases and postoperative complications (LE 3).[17,20]

Histopathological examination

Histopathological confirmation of the primary lesion can be done either by cytology or histology using any of the following methods:

- incisional biopsy
- tissue core biopsy
- fine-needle aspiration
- brush biopsy
- excisional biopsy (therapeutic in some cases).

Small or superficial penile biopsies are difficult to classify with regard to histological type, grade, invasion and other pathologic parameters related to prognosis. A study of 57 consecutive patients with SSC of the penis compared the pathologic information obtained from biopsies and penectomies.[21] In 17 cases (30%) there was a biopsy-penectomy discordance of histologic types, especially of verruciform and mixed carcinomas. Biopsies failed to identify the correct histologic grade in 30%. A higher grade was usually identified in penectomy specimens. Because biopsies were superficial, the deepest point of invasion could not be determined in 91%. Vascular invasion was identified in biopsies in only 1/8 patients (LE 3).[21] These findings indicate that data from biopsies may be insufficient to inform decisions about treatment and prognosis.[21] It has been suggested that such decisions should preferably be based on a resected specimen.[22]

Guidelines and recommendations have been proposed for the fixation and processing of specimens for histological diagnosis and reporting of penile cancer.[3,23,24] It is important that the surgical specimen is properly pinned and orientated so that the pathologist can identify the various true surgical margins, in order to perform the necessary sections and to locate each sample adequately.[24]

The pathology report should provide information useful for therapy and prognosis, therefore it should include all the factors which may be predictive with regard to lymph node metastases, local or distant tumor recurrence, disease-free and cancer-specific survival (LE 3):[22,25-29]

- anatomical site and size of the tumor
- histological type or subtype
- grade
- pattern of growth
- front of invasion
- depth of invasion
- tumor thickness
- resection margins
- lymphovascular invasion
- perineural invasion.

Grading

Grading is important with regard to the degree of local tumor extension, as well as the risk of inguinal node metastases.[3,22,30,31]

The ''classical'' grading is based on the degree of cell anaplasia (Table 1).[3] A common approach is to grade penile cancer as 1 = well, 2 = moderately and 3 = poorly differentiated. Well differentiated carcinoma shows no evidence of anaplastic cells, moderately differentiated carcinomas contain less than 50% and poorly differentiated tumors contain more than 50% of anaplastic cells.[28]

Table 1: Standard histological grading of squamous cell carcinoma of the penis.[3]	
Grade 1	Well differentiated cells with typical intracellular bridges and marked keratinization with the production of typical keratin pearls. The degree of anaplasia and the number of mitotic figures are low
Grade 2	Single cell keratinization, no keratin pearls and a higher number of mitoses and anaplastic cells
Grade 3	Poor cell differentiation with numerous mitoses and complete lack of keratinisation
Grade 4	Undifferentiated carcinomas

Velazquez et al.[32] and Cubilla[22] reported a method to grade penile SCC, in which Grade 1 is an extremely well-differentiated carcinoma, with minimal deviation from the morphology of normal or hyperplastic squamous epithelium. Grade 3 are tumors showing any proportion of anaplastic cells, identified as solid sheets or irregular small aggregates, cords or nests of cells with little or no keratinization, high nuclear cytoplasmic ratio, thick nuclear membrane, nuclear pleomorphism, clumped chromatin, prominent nucleoli and numerous mitoses. In the grade 2 category are the remainder of tumors. The authors stated that grading the extremes of the spectrum is simple and reproducible (LE 3).[22,32]

In a retrospective analysis of 239 patients with SCC of the penis a more sophisticated histological grading system with 4 grades was proposed by Maiche et al, based on the degree of keratinization, cell atypia, mitotic activity and the amount of inflammatory cell infiltrate. The tumors were grade 1 in 50% and grade 2 in 29% of cases. Patients with grade 1 tumors had a favourable prognosis and more than 80% were long-term survivors (LE 3).[3,33]

Cubilla noted that there has been no study comparing the various methods used for grading penile cancer. Although tumor heterogeneity (more than one grade present in the same tumor) is a feature of many malignancies, this has not been studied in penile cancer.[22]

A study of 64 patients who underwent partial or total penectomy based on the extent of tumor found that higher grade lesions were more likely to involve the penile shaft. The maximum proximal histological extent was 5 mm for grades 1 and 2, and 10 mm for grade 3 tumors, with no discontinuous spread. Only 12 of the 64 tumors had microscopic extension beyond the gross tumor margin; most of these (83%) were high-grade lesions and all lesions with positive margins at 10 mm were grade 3 lesions. The authors concluded that during penectomy a 10-mm clearance is adequate for grade 1 and 2 lesions, and 15 mm for grade 3 tumors. Considering that the vast majority of tumors (about 80%) have minimal (<5 mm) microscopic extension, if any, beyond the visible proximal edge of the lesion, these findings have considerable therapeutic implications, indicating that local excision or partial penectomy may be adequate (LE 3).[30]

In a study of 51 men with penile cancer staged with MRI and selected for conservative surgery, histopathological evaluation showed that the surgical margin was within 10 mm of the tumor edge in 48%, and within <20 mm in 90% of cases. Only 6% of patients had tumor involvement of the surgical margin and had further surgery. At a median followup of 26 months local tumor recurrence occurred in 4% of the patients. The authors concluded that a traditional 2 cm excision margin is unnecessary for treating SCC of the penis, and that conservative techniques offer excellent oncological control (LE 3).[31]

There is no consensus about the criteria for grading and the proportion of anaplastic cells required to classify a tumor as high-grade. The incidence and management of heterogeneous tumors (harboring more than 1 histologic grade) are not well established. Chaux et al. studied a total of 117 penectomy and circumcision specimens with bilateral inguinal lymph node dissection. They estimated the proportions of grades using visual and digital-based techniques (slides were scanned and the corresponding areas measured with image-editing software). There was no significant difference between the visual and digital measurement

systems. They identified heterogeneous tumors in 62 cases (53%). The majority of the heterogeneous tumors were composed of a combination of grades 2 and 3 (68%). Metastases were significantly more frequent in tumors harboring any proportion of grade 3 compared to tumors without grade 3 (58% vs. 14%). Any proportion of grade 3 was associated with a significant risk of nodal metastasis. The authors recommended that, when histologically evaluating penile carcinomas, a careful search should be made for areas of grade 3, and suggested that any focus of grade 3 should be sufficient to grade the neoplasm as a high-grade tumor (LE 3).[34]

A study of 81 surgically treated patients (25 with recurrent and 56 with nonrecurrent penile SCC) compared recurrent tumors at the time of primary diagnosis and of recurrence and showed that in 24% of cases there was a higher grade tumor in the recurrence, especially, in patients treated with local excision and circumcision. Recurrent tumors also invaded into deeper anatomic levels than nonrecurrent tumors, had a higher incidence of inguinal lymph node metastasis (79% vs. 49%) and lower cancer-specific survival (46% versus 76%). The authors concluded that conversion from low to high-grade carcinoma was related to significant mortality and suggested that the identification of adverse prognostic factors should be the basis for aggressive initial therapy to prevent recurrence. Re-excision of the recurrent tumor permitted control of the disease only in one third of the patients (LE 3).[35]

TNM-staging system – proposed modification

Accurate tumor staging is essential in the management of malignancies, because it guides treatment selection and gives an indication of prognosis. It is important that the different stages should correlate with significant differences in prognosis. A lack of sufficient ability to discriminate between levels of outcome indicates that revision of the staging system is required.

Historically, there have been several staging systems for carcinoma of the penis.[36] The Jackson classification, with 4 categories based on operability of the tumor and nodal metastases, was introduced in 1966 and was the most commonly used staging system until the TNM (tumor, nodes, metastases) classification was introduced in 1968 (Fig. 1).[37] The TNM system was revised in 1978 and 1987, but has subsequently remained unchanged.[38-40]

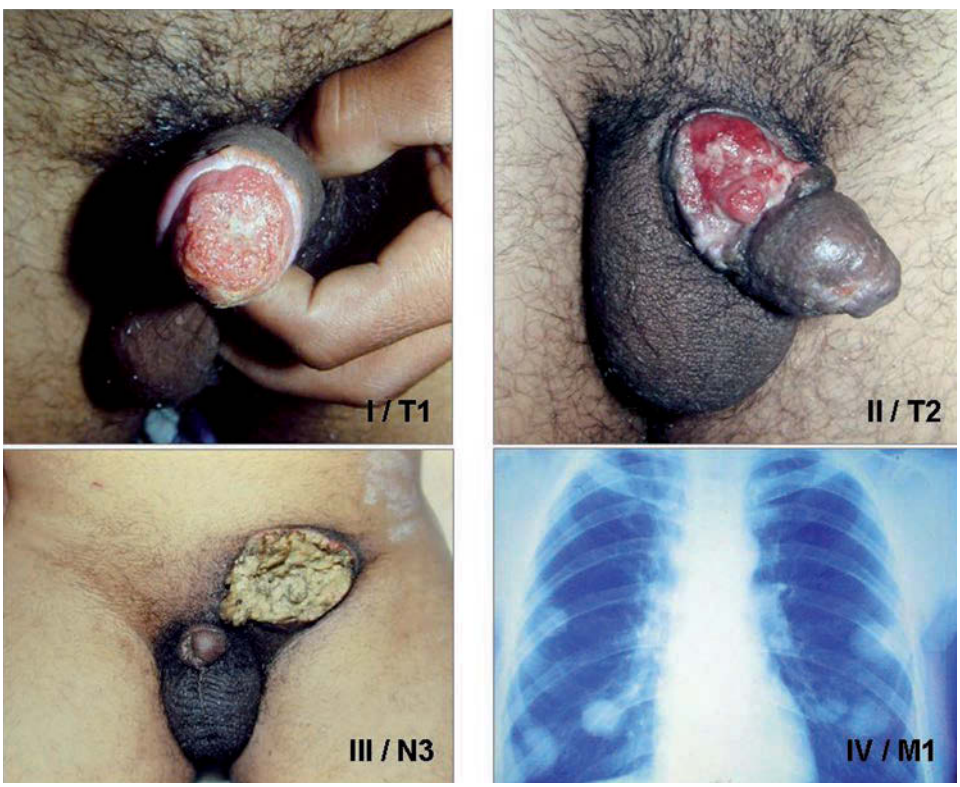

Fig. 1: *Jackson staging system versus TNM staging system.*

Maiche et al. observed certain shortcomings in the various staging systems. In a study of 239 patients they grouped the subjects into the different classification systems, including the 1978 and 1987 TNM systems, the Jackson as well as the Heidelberg systems. They developed a new staging system, with better discrimination of survival rates according to the different stages (LE 3).[41]

A study of 118 patients classified with the 1978 TNM staging system showed statistical significance in univariate analysis, but in multivariate analysis only the grade and N-category were independent prognostic factors of survival. A stage grouping consisting of 3 stages was proposed, with 5-year survival probabilities for stages 1, 2 and 3 of 93%, 55% and 30%, respectively. The revised 1987 TNM staging system was analyzed with the previous method used in this study, and prognostically important and clinically useful parameters, such as the size of the primary tumor and evidence of fixation of the regional lymph nodes, were discarded. The authors concluded that the changes in the 1987 revised TNM classification seemed to have little relevance to clinical staging, and that it should be considered a histopathological classification only (LE 3).[7]

A study of 145 patients with penile carcinoma staged according to the 1978 TNM system and treated with penectomy and lymphadenectomy found that the T-stages were not significant predictors for the incidence of lymph node metastasis, disease-free or overall survival (LE 3).[25]

In a study of 76 patients McDougal proposed a classification system based on the grade of differentiation and the depth of invasion of the primary lesion, which correlated well with the risk of inguinal node metastases as well as survival (Table 2) (LE 3).[42]

Table 2: Staging system proposed by McDougal.[42]

Stage	Definition	Lymphadenectomy done	3-year survival (%)
1	Grade 1, superficial, no extension into subcutaneous tissue	None	100
2A	G1-2, locally invasive, without involvement of corpus spongiosum or cavernosum	None	100
2B	G3, or invasion into corpus spongiosum or cavernosum	None	17
		Immediate	92
		Delayed	33
3	Palpable inguinal nodes persisting after 6 weeks of antibiotics	Immediate	75
		None or delayed	33
4	Inoperable inguinal nodes, ilac node involvement, distant metastases		

In a study of 35 patients with SCC of the penis Heyns et al.[43] compared the 1978 clinical TNM staging system (in which the diameter of the primary tumor and the clinical extent of invasion were considered) with a modified T-system in which the histological degree of differentiation and pathological extent of tumor invasion were combined (T1 = grade 1-2, invasive through dermis; T2 = any grade, invasion of corpus spongiosum or cavernosum; T3 = any grade, invasion of urethra; T4 = grade 3, regardless of invasion). The modified T-staging system (histological grade plus pathological extent of invasion) provided the best predictive distinction with regard to inguinal lymph node metastases (LE 3).[43]

A single-institution study of 100 consecutive patients classified with the current TNM-staging system noted that men with T3 tumors had a better

survival than those with T1 and T2 disease. The possible explanation was that tumors growing into the urethra (classified as T3) do not behave as aggressively as those invading corporal tissue (T2). The authors suggested that the T-stage of the current TNM system should be revised (LE 3).[44]

Although a previous report by Horenblas et al.[45] had discarded primary penile tumor size as a prognostic factor, Brennhovd et al.[46] found that among patients with G1-2pT1 carcinomas, 2 of 3 with tumors >3 cm in diameter had lymph node metastases. The authors suggested that as the cancer grows to a certain volume or surface area, the probability of lymph node metastases increases, independent of the extent of the primary tumor and its grade (LE 3).[46]

Accurate clinical staging can be difficult, because several categories are defined by anatomical structures that can not readily be identified by physical examination or imaging.[39] The T3-category is defined by invasion of the urethra or prostate. However, histological invasion of the anterior urethra occurs in 25% of cases and is not necessarily associated with a poor outcome. Invasion of the prostate by penile cancer is extremely unusual in the absence of regional extension (T4) or systemic metastases.[22,39,40,47,48]

The prognosis of patients with tumor invasion of the corpus spongiosum is better than those with invasion of the corpus cavernosum.[42,49,50] Rees et al.[51] reported on 72 patients with pT2 tumors. Compared to those with spongiosal invasion only (pT2a), those with tunical or cavernosal involvement (pT2b) had higher local recurrence (35% vs 17%) and mortality rates (30% vs 21%) after a mean follow-up of 3 years. The pT2b tumors had a greater depth of invasion (15 mm versus 8 mm) but a similar incidence of lymph node involvement (40% vs 44%), lymphovascular invasion (30% vs 27%) and metastases (11% vs 10%) (LE 3).[51]

A retrospective analysis of the records of 513 patients treated between 1956 and 2006 confirmed the difference between tumor invasion of corpus spongiosum and cavernosum. It also confirmed that there were no differences in long-term survival between T2 and T3, and no significant differences between N1 and N2 in the 1987-2002 TNM classification (LE 2). A new TNM classification was therefore proposed (Table 3). The authors suggested that the new classification is much more appropriate than the present TNM categories, but conceded that it needs confirmation in other studies.[39]

In their analysis of 513 patients Leijte et al. reported a 5-year disease-specific survival (DSS) of 80.5% in the whole group at median followup of 58.7 months. There was no significant difference in survival between T2 and T3 tumors according to the 1987-2002 TNM classification.[39,40] There was a significant difference in DSS between patients with tumor invading the corpus spongiosum only (77.7%) and tumor invading the corpora cavernosa (52.6%). The probable explanation is that the capacity of a tumor to break through the relatively thick tunica albuginea covering the corpora cavernosa reflects more invasive properties.[40]

Leijte et al. proposed certain modifications to the T-staging system to improve prognostic stratification (Table 3). They found a significant difference in the risk of inguinal node metastases as well as disease-specific survival between all T-categories when defined according to this proposal (Table 4) (LE 3).[39,40]

Table 3: Comparison of current T-staging system and proposed T-categories.[39,40]		
	Current T-category (TNM 2002)	**Proposed modification of T-category**
Tx	Primary tumor can not be assessed	Primary tumor can not be assessed
T0	No evidence of primary tumor	No evidence of primary tumor
Tis	Carcinoma in situ	Carcinoma in situ
Ta	Noninvasive verrucous carcinoma	Noninvasive verrucous carcinoma
T1	Tumor invades subepithelial connective tissue	Tumor invades subepithelial connective tissue
T2	Tumor invades corpus spongiosum or cavernosum	Tumor invades corpus spongiosum
T3	Tumor invades urethra or prostate	Tumor invades corpus cavernosum
T4	Tumor invades other adjacent structures	Tumor invades adjacent structures (including prostate)

Table 4: Percentage of node-negative disease in the current and proposed T-categories.[39,40]		
	Current T-category (TNM 2002) (%)	**Proposed T-category (%)**
Tis/Ta	98.1	98.1
T1	87.6	87.6
T2	57.5	65.7
T3	57.9	42.7
T4	0	0

The presence and extent of regional lymph node metastases are the most important determinants of survival in patients with penile SCC.[52] All inguinal lymph nodes, irrespective of anatomical location, are considered first line regional nodes. All pelvic nodes are considered second line regional nodes.[53,54]

In the 1987 TNM staging system the division between the N1 and N2 groups is based on the number of involved nodes (1 versus 2 or more) and/or bilateral inguinal involvement. Several studies have reported that an increased number of tumor-positive lymph nodes is associated with decreased survival (LE 3).[8,55,56] On multivariate analysis of factors influencing survival Pandey et al. found that only 4 or more positive inguinal nodes had a significantly negative effect on survival (LE 3).[57] In a similar study Ravi defined greater than 3 positive inguinal nodes as an adverse prognostic factor (LE 3).[58] Several studies are available in which the survival of patients with bilateral node involvement was significantly worse than that of patients with unilateral involvement (LE 3).[8,55-57,59,60]

The current TNM-classification makes a distinction between superficial inguinal nodes (located between Scarpa's fascia and the fascia lata) and deep inguinal nodes (located around the fossa ovalis). In clinical practice no distinction between the two can be made. Even in histopathological analysis of the lymphadenectomy specimen, it is often diffcult to distinguish between the two. In the current classification a single tumor-positive superficial node is classified as N1, while a tumor-positive deep inguinal node is classified as N3. In contrast to the 1978 TNM version, the presence of a fixed inguinal node is not categorized as a separate entity. Fixed inguinal nodes are generally considered inoperable and have an ominous prognosis, so it seems contradictory that a fixed, but single and unilateral, tumor-positive node is classified as N1.[39,40]

Leijte et al. retrospectively analyzed the records of 513 patients treated between 1956 and 2006. Using the 1987-2002 TNM classification, they found no significant survival difference between N1 and N2 categories. The 5-year DSS in the N1 and N2 category was 70.2% and 58.3% years, respectively The authors proposed modifications of the TNM staging classification to facilitate clinical staging and to improve prognostic stratification (Table 5). Using their proposed modification of the N-staging system, the 5-year DSS in the proposed N1, N2 and N3 categories was 77%, 54% and 11%, respectively. The difference in survival between all categories was significant (LE 3).[39,40]

Extracapsular node extension (ENE) of malignancy has been reported to negatively influence survival in patients with penile cancer.[57,58,61] However, ENE was not considered in the study of Leijte et al, since this information was only available in part of their patient population. They pointed out that, although their series contained a relatively large number of patients, the data are from a single institution, therefore critical appraisal and validation in other patient groups is required.[39]

Table 5: Comparison of current N-staging system and proposed N-categories.[39,40]

	Current N-category (TNM 2002)	Proposed modification of N-category
Nx	Regional lymph nodes can not be assessed	Regional lymph nodes can not be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Metastasis in a single superficial inguinal lymph node	Unilateral inguinal metastasis, mobile
N2	Metastasis in multiple or bilateral superficial lymph nodes	Bilateral inguinal metastasis, mobile
N3	Metastasis in deep inguinal or pelvic lymph node(s), uni- or bilateral	Fixed inguinal metastasis, or pelvic lymph node metastasis

In their comment on this proposal Zhu et al.[62] stated that assessment of the mobility of lymph nodes is subjective, and pointed out that in other cancer types lymph node mobility is seldom included in the N-category. Because the size of the metastatic inguinal lymph node is associated with poor prognostic factors, such as extranodal extension and pelvic lymph node metastases, they suggested a clinical N-category based on the long diameter of the lymph node instead of its mobility.[62] Leijte et al. replied that a fixed metastatic inguinal mass that is considered inoperable has a poor prognosis, even in the absence of pelvic lymph node or distant metastasis. For this reason they proposed classifying these cases as N3 regardless of the pelvic node status. Also, in their study they did not find a significant difference in survival between patients with 2 or fewer tumor positive inguinal lymph nodes versus 3 or more, whereas unilateral versus bilateral node involvement significantly predicted survival. They suggested that it is easier to differentiate between a fixed inguinal mass and a mobile lymph node than between a superficial and a deep inguinal node. From a histopathological standpoint a nonmobile inguinal lymph node will in most cases indicate the presence of extracapsular invasion.[62]

Inguinal nodes – clinical staging

It is well established that the presence and extent of lymph node metastases are the most important predictors of survival.[8,63,64] Physical examination is the most important means of diagnosing inguinal lymph node involvement. At initial presentation, clinically palpable inguinal lymph nodes are present in 28%–64% of patients with penile carcinoma. In 47%–85% of these patients, lymphadenopathy is caused by metastatic invasion, while inflammatory reaction accounts for the remainder. Approximately 25% of patients

with palpable inguinal metastases will have bilateral palpable disease, with 75% having unilateral palpable node involvement.[8,64,65]

The characteristics that should be analyzed regarding palpable nodes or mass(es) are:

- diameter
- uni- or bilateral localization
- number in each inguinal area
- mobile or fixed
- relationship to other structures (e.g. skin, Cooper's ligaments) with respect to infiltration, perforation
- presence of oedema of leg and/or scrotum.

Physical examination to predict pathologically involved lymph nodes is not reliable, with a false-negative rate of 11%-62%. Other staging strategies, including noninvasive imaging (US, CT and MRI) and minimally invasive methods such as fine needle aspiration cytology (FNAC) and sentinel lymph node biopsy (SLNB) are also associated with false-negative findings.[54,66]

In a study of 118 patients with SCC of the penis staged with clinical examination, lymphography, CT and FNAC, when the regional lymph nodes were categorized simply as positive or negative, 80% of the nodes were classified correctly and 20% incorrectly (13% were false positive and 7% were false-negative). Regional lymph node invasion that escaped clinical examination was not detected by any imaging examination or FNAC. Positive findings were found only in patients with clinically suspected nodes. The authors concluded that classification of regional nodes by clinical examination is not significantly improved by imaging studies (LE 3).[5]

Patients with clinically palpable lymph nodes should undergo imaging with abdominopelvic CT to define the extent of disease, since pelvic adenopathy (or fixed masses) may be indications for neo-adjuvant chemotherapy prior to surgery.[67]

There is increasing evidence that the metastatic potential of T1G2 tumors is higher than expected.[54,68] In a recent analysis of more than 700 patients from 2 centers it was calculated that the risk of nodal metastasis at presentation or during followup was 6.3% in T1G1, 12.2% in T1G2 and 44.6% in T1G3 tumors. This indicates that surgical nodal staging rather than surveillance is indicated for T1G2 tumors.[39]

Inguinal nodes - surgical staging

In patients with no clinically palpable nodes (cN0) 12%-20% will harbour occult metastases.[3,4,69,70] Several studies have shown the sensitivity of clinical node staging to be 40%–60% with a false-negative rate of around 10%–20%.[42,71]

In patients with nonpalpable inguinal lymph nodes, surgical staging can be performed by complete inguinal lymph node dissection (ILND). There is evidence that early ILND significantly improves cancer-specific survival.[69] In one study, men with penile cancer who underwent lymphadenectomy with impalpable positive nodes had a survival rate of 84%, compared to 33% in those who underwent lymphadenectomy for palpable disease (LE 3).[42] However, the therapeutic benefits of early ILND in all patients (where 80%-90% of procedures may be unnecesssary) have to be weighed up against the risk of postoperative complications in 24%–87% of patients and mortality in about 3%.[65,72]

Ravi et al. evaluated biopsies of all identifiable nodes in the inguinal region in 52 patients with invasive penile carcinoma. The sensitivity of their "inguinal pick" procedure in detecting regional metastases was only 72%. There was no morbidity, but a negative result did not guarantee absence of regional metastases (LE 3).[73]

In a study of 66 patients the presence of metastatic nodes was influenced by both tumor stage and grade. None of the patients with T1GI tumors developed nodal metastases, and 80% of the patients with T2-3G2-3 tumors developed metastatic lymph nodes. In the remaining 22 patients with T1G2-3 and T2G1 tumors, 36.4% showed metastatic lymph nodes.[49] Similar findings in other studies led to the recommendation of risk stratification, where ILND is performed in high-grade, high-stage tumors, and a policy of surveillance is followed for low-grade, low-stage tumors. However, the problem lies with the intermediate group, where management remains controversial.

With regard to the question whether bilateral or unilateral lymphadenectomy should be performed in patients at high risk of nodal metastases, a prospective study of 50 patients submitted to routine bilateral superficial and deep lymphadenectomy showed that spread to the right side, left side and both sides occurred in 24%, 30% and 46% of cases respectively. For this reason it was proposed that bilateral lymphadenectomy should be the standard.[74]

In a retrospective series of 37 patients with penile cancer, local recurrence and disease progression occurred in 43% of T1 N0 lesions.[75] A retrospective review of 20 patients with pT1G2 penile SCC found that the metastatic risk was 44% in those with an initially negative groin. The authors recommended surgical staging of inguinal lymph nodes in patients with pT1G2 penile SCC (LE 3).[76]

There is evidence that the metastatic potential of T1G2 tumors is higher than expected.[54,68] A study of 56 consecutive patients with penile cancer who underwent surgical inguinal lymph node staging showed inguinal metastases in 7.7% of low risk (pT1G1-2), in 28.6% of intermediate risk (pT2-4G1-2) and in 75% of high risk (T-anyG3) tumors.[77] In an analysis of more than 700 patients from 2 centers the risk of nodal metastasis at presentation or during followup was 6.3% in T1G1, 12.2% in T1G2 and 44.6% in T1G3 tumors (LE 3). Consequently, these authors recommended ILND for T1G2 and all G3 tumors.[39]

In a single-institution study of 100 consecutive patients, those with palpable nodes had pathologically confirmed metastases in 72%, whereas 18% of those with impalpable nodes who had lymphadenectomy according to the above risk-stratification guidelines had lymph node disease. The authors concluded that the current guidelines are limited in predicting those patients with micrometastatic disease, with the result that 82% of patients undergo unnecessary prophylactic lymphadenectomy.[44]

To improve the accuracy of predicting inguinal lymph node metastases, a nomogram has been developed which incorporates 8 clinical and pathologic variables (tumor thickness, microscopic growth pattern, histological grade, presence of vascular or lymphatic embolisation, infiltration of the corpora cavernosa, corpus spongiosum or urethra, and clinical stage of inguinal lymph nodes). The nomogram was developed from a database of 175 patients, and has to be validated in other patient cohorts.[65,72]

In a study of 193 patients who underwent penectomy/circumcision and bilateral lymphadenectomy for invasive SCC Chaux et al.[78] proposed a Prognostic Index (PI) to estimate the incidence of inguinal node metastasis. The PI (ranging from 2 to 7) consisted of the addition of numerical values given to histologic grade (1 to 3), tumour invasion (lamina propria =1, corpus spongiosum = 2, corpus cavernosum = 3), and the absence or presence of perineural invasion (PNI) (0 or 1). The rate of metastasis according to PI scores were: 4 = 20%; 5 = 50%; 6 = 66%; and 7 = 79%. On logistic regression analysis the PI was the best predictor of inguinal node metastasis and survival. The authors suggested that inguinal node dissection may be unnecessary for PI of 2-3 and may be mandatory for PI 5-7, whereas patients with PI of 4 should be individually assessed for nodal dissection.[78]

- **Sentinel lymph node biopsy (SLNB)**

Gould et al. first coined the term sentinel lymph node (SLN) in parotid tumors in 1960.[79] The theory was further developed in penile cancer by Cabanas.[80] Lymphangiographic studies demonstrated drainage into a specific lymph node center, the so-called SLN, which is the first filter in the lymphatic pathway and the most likely regional node to harbor metastatic carcinoma.[81]

Sentinel lymph node biopsy (SLNB) has been used in patients with various malignancies, including melanoma and cancers of the breast, vulva, cervix, penis, prostate, head and neck, thyroid, lung, stomach and colon. Focused analysis of the SLN may reveal cancer that might otherwise go undetected by conventional surgical and pathological methods.[82]

The role of SLNB in penile cancer remains controversial. Several early studies suggested that there was an unacceptably high rate of false-negative

results from SLNB, but these studies involved small sample sizes and did not use lymphoscintigraphy and blue dye to localize the SLN.[83-87]

In 1988, Catalona proposed a modified bilateral inguinal lymphadenectomy in which the saphenous vein is preserved together with reduction of the lateral, distal and proximal margins of dissection. The procedure was performed on 12 consecutive men, of whom 5 were identified with nodal metastasis. No major complications occurred. With a followup of 14 to 72 months no patient had recurrent disease (LE 3).[88]

In a prospective study, Lopes et al. evaluated 13 patients submitted to modified bilateral ILND. Two of these patients developed regional lymph node metastases within 13.2 months. The authors concluded that Catalona's procedure was not reliable (LE 3).[89]

A retrospective review of 20 consecutive patients who underwent extended SLN dissection showed that 5 had inguinal metastases at a median followup of 10 months. The authors cautioned that extended SLN dissection is still associated with a significant false-negative rate (25%) (LE 3).[85]

Perdonà et al. compared elective bilateral lymph node dissection with SLNB in penile carcinoma and found similar rates of nodal metastases (39% vs 36%), but SLNB was associated with considerably lower post-operative morbidity.[90]

- **Dynamic sentinel lymph node biopsy (DSLNB)**

Dynamic sentinel lymph node biopsy (DSLNB) was developed by Morton using "blue dye" and Krag using radioactive tracers to identify the SLN.[81] Currently, DSLNB is performed by intradermal injection of ^{99m}Technetium nanocolloid around the primary tumor, preoperative lymphoscintigraphy, and intraoperative identification of the SLN with the aid of intradermally administered patent blue dye and a gamma ray detection probe (Figs. 1-3). Histopathological examination of SLNs include serial sectioning and immunohistochemical staining.[91]

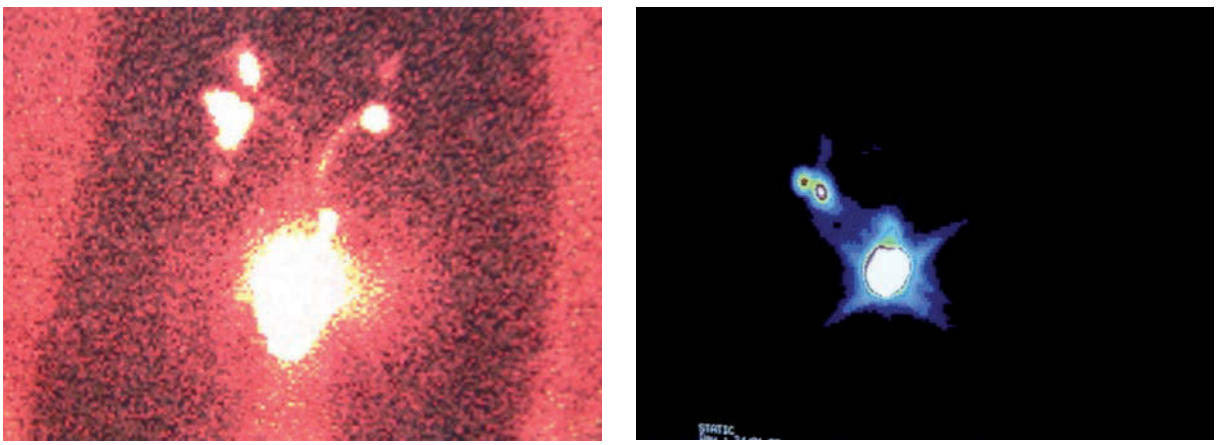

Fig. 2: *Preoperative lymphoscintigrams obtained after injection of ^{99m}-Technetium-labeled nanocolloid around the primary tumor, showing radio-activity in the penile lesion and sentinel lymph nodes.*

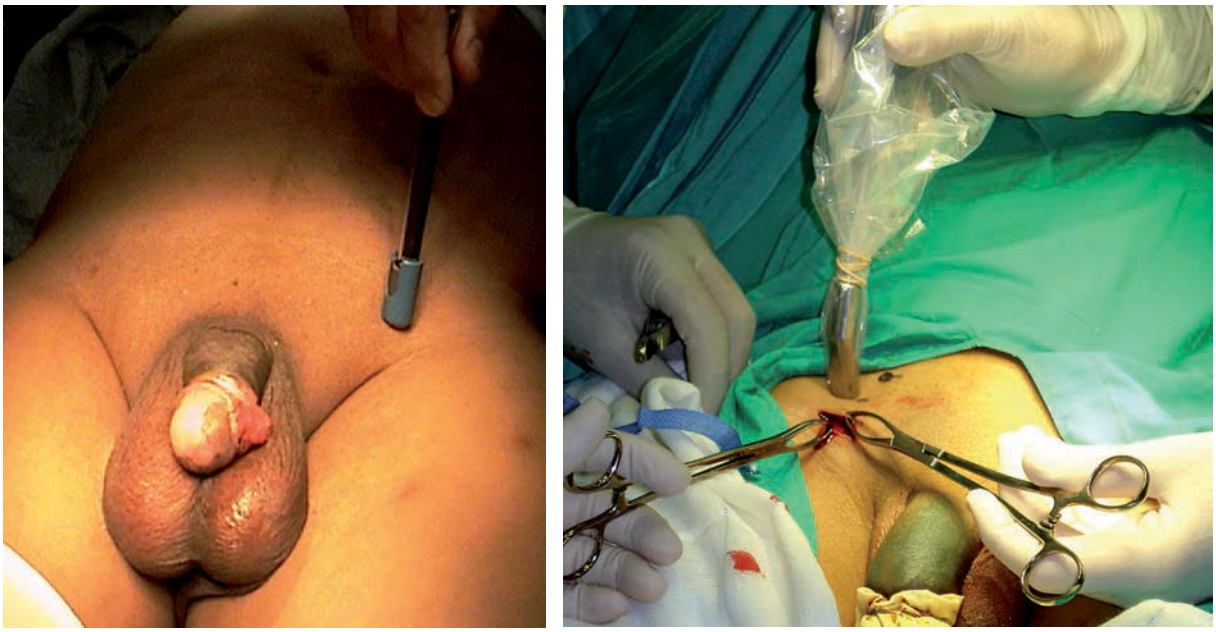

Fig. 3: *Pre- and intra-operative use of a gamma probe to localize radio-labeled sentinel lymph nodes.*

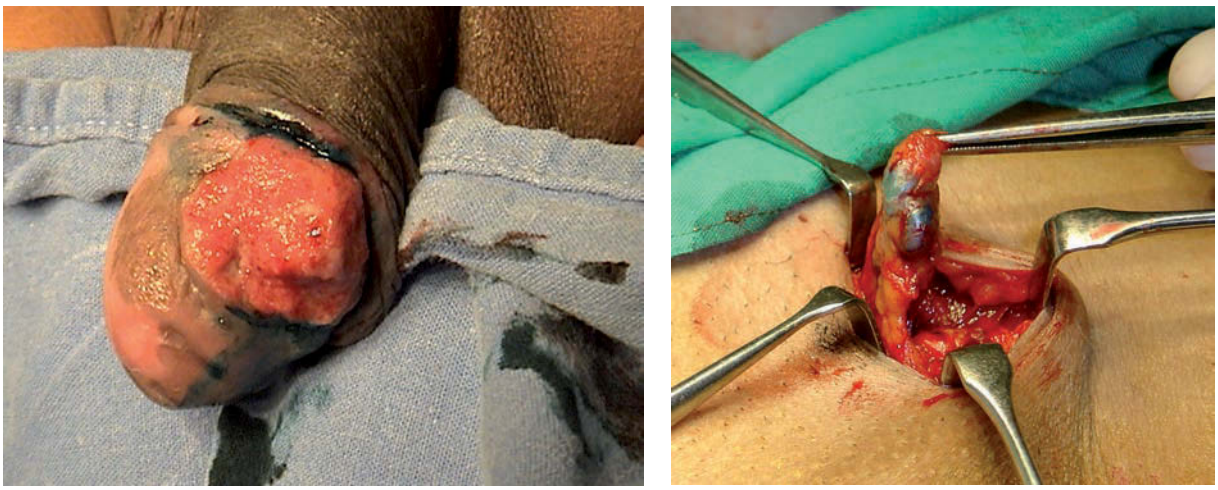

Fig. 4: *Primary penile lesion with intradermally injected patent blue dye, and inguinal lymph node stained with blue dye.*

A study of lymphoscintigraphy in 74 patients with cN0 SCC of the penis identified the following pitfalls: inguinal skin contamination during injection, intracavernous administration, and delayed lymph node filling (LE 3).[92]

A prospective study of 27 patients evaluated with injection of sodium phytate technetium as tracer and gamma probe scanning to identify inguinal nodes reported a sensitivity of 25% and a false-negative rate of 42.8%. The authors concluded that the isolated gamma probe technique for DSLNB has a very low sensitivity and a high false-negative rate (LE 3).[93] Tanis et al. reported a false-negative rate of 22% (LE 3).[91] An evaluation of DSLNB performed over a period of 10 years in 140 patients with clinically node-negative groins reported a false-negative rate of 16% and complications in 8% of the operated groins (LE 3).[87] It has been pointed out that this false-negative rate of 16% needs to be compared with the rate of micrometastatic disease of 18% in a large prospective series of clinically node negative patients.[44] The implication is that in cN0 patients DSLNB has the same false-negative rate as clinical examination.

A study of DSLNB using blue dye and radiocolloid in 9 patients with penile cancer reported a sensitivity of 80% and a false-negative index of 20% (LE 3).[94] An evaluation of DSLNB with ^{99m}-Technetium labeled sulfur colloid and isosulfan blue dye in 21 patients, and blue dye only in 10 patients, reported a sensitivity per groin for cancer detection of 71%. The authors concluded that preoperative lymphoscintigraphy and dynamic sentinel node biopsy as currently performed remain insufficient for detecting occult inguinal disease (LE 3).[95]

A study of DSLNB in 15 patients with penile cancer reported high reliability and negative predictive value (LE 3).[96] Jensen et al. reported a single-centre experience with DSLNB using ^{99m}-Technetium nanocolloid but no blue dye injection in 97 procedures performed in 52 patients. The false-negative rate was 9%, sensitivity 91%, NPV 97.5%, and minor early complication rate 4% (LE 3).[97] A study of DSLNB in 17 consecutive patients with bilateral cN0 penile cancer showed a sensitivity of 88% and NPV of 100% (LE 3).[98] A study of DSLNB compared with modified radical lymphadenectomy in 18 patients reported a sensitivity of 66%, specificity of 79% and false-negative rate of 0. The authors concluded that the optimal lymphoscintigraphy technique is still in evolution and requires further optimization at high volume centers (LE 3).[99]

The group at the Netherlands Cancer Institute has been performing DSLNB in clinically node-negative patients with penile carcinoma since 1994. Over time, several modifications were made to reduce the false-negative rate and increase sensitivity. Comparing patients treated from 1994 to 2001 with those treated from 2001 to 2004 showed that the false-negative rate decreased from 19.2% to 4.8%, while the complication rate dropped from 10.2% to 5.7%. (LE 3).[100]

DSLNB is not useful in men with palpable inguinal nodes. In a study of DSLNB in 23 patients with clinically palpable inguinal lymph nodes Heyns and Theron reported a false-negative rate of 13% (LE 3).[101] It has been suggested that extensive metastatic involvement of a sentinel node can lead to blocked inflow and rerouting of lymph to a "neo-sentinel node" that may not yet contain tumor cells, causing a false-negative result.

Recently introduced hybrid SPECT/CT scanners provide both tomographic lymphoscintigraphy and anatomic detail. A study of 17 patients with unilateral palpable and cytologically proven metastases in the groin evaluated with conventional lymphoscintigraphy and SPECT/CT before DSLNB confirmed the concept of tumor blockage and rerouting in 76% of the groins with palpable metastases (LE 3).[102]

The low false-negative rate recently reported by the group at the Netherlands Cancer Institute resulted from the following refinements:[46,103-105]

- inguinal US with FNAC to detect subtle architectural changes in nonpalpable positive lymph nodes that could result in the redistribution of lymphatic flow;
- direct palpation of the inguinal area or visualization of nodes stained with blue dye to identify nodes that were not detected via gamma emission due to obstruction of lymphatics by cancer;
- surgical exploration of groins with low or no signal subsequent to preoperative or intraoperative studies;
- routine serial sectioning of the involved lymph nodes along with cytokeratin immunohistochemistry to increase the sensitivity of pathologic detection.

Data coming from breast cancer recommendations concerning DSLNB suggest that surgeons should perform at least 20 procedures per year. Moreover, it is recommended that in the learning curve the first 20 DSLNBs should be assisted by an experienced surgeon. Before routinely adopting the procedure, surgeons should complete 20 procedures followed by full lymphatic clearance with a false-negative rate of <5%. Considering the rarity of penile carcinoma, it will be extremely difficult to fulfill these requirements outside of a few high volume referral centres.[16,65,87]

The clear advantage of DSLNB is the reduced morbidity, reported at 8%, versus as high as 88% for standard ILND. A recent 10-year review by Kroon et al. indicated that, when patients have only micro-metastases (2 mm or less) in the SLN, all other inguinal nodes should be clear of tumor,

and may therefore be spared further nodal dissection (LE 3).[106]

The potential disadvantages of DSLNB include (1) the relatively high false-negative rate, (2) the requirement for considerable expertise and collaboration between specialists in surgery, pathology and nuclear medicine, (3) the time required to learn and gain experience with the procedure, (4) the high cost (estimated at 11,000 Euro per case) and (5) the necessity for quality control.[107,108]

It has been stated that DSLNB remains the best minimally invasive staging modality for cN0 penile cancer.[64] Conversely, it has been suggested that until the false-negative rate of DSLNB becomes zero, complete ILND should remain the reference standard. Ideally, a randomized study of DSLNB against standard management according to EAU guidelines with disease-free survival as the primary endpoint should be conducted, preferably in a multi-institutional setting.[107,109]

Where DSLNB is not feasible, superficial or modified ILND with intraoperative frozen section represent alternative strategies for defining the presence of microscopic metastases with relatively low morbidity.[110,111]

Lymph nodes – imaging

▪ Ultrasound

High resolution ultrasound (US) probes are able to detect subtle findings of early malignancy such as asymmetric thickening and focal lobulations in the lymph node cortex as well as the later manifestations of disease such as cortical thickening and loss of the hilum.[112] These changes in the architecture often occur before the node enlarges.

Criteria used for the identification of abnormal groin nodes by US include:[113]

- increased size
- abnormal shape
- rounded with a short/long axis ratio of less than 2
- eccentric cortical hypertrophy
- absence of an echogenic hilum
- hypoechogenicity of the node compared with adjacent muscle
- lymph node necrosis
- abnormal peripheral vascularity using power Doppler.

The appearances of nodes containing metastases have some overlap with reactive or infected lymph nodes, and it is well recognized that micrometastatic disease within nodes can not be accurately identified by US alone. The criteria for suspected malignancy are sensitive but not specific, thus increasing false-positive US findings. The major benefit from US is in identifying nodes that are infiltrated with tumor but are bypassed by both nanocolloid and blue dye during DSLNB.[113]

▪ Fine-needle aspiration cytology (FNAC)

The role of fine-needle aspiration cytology (FNAC) guided by penile and pedal lymphography was evaluated in a study of 29 cases. Aspiration was performed under fluoroscopic or CT guidance using a 22-23-gauge needle. The accuracy of FNAC in identifying the true stage of the disease was 100%. The authors concluded that positive cytology is conclusive of node metastases, but negative aspirations do not guarantee the absence of metastases (LE 3).[114] FNAC guided by penile and pedal lymphography was reported as an innocuous, accurate, easy, and inexpensive diagnostic procedure. Since radiopaque contrast medium opacifies the nodes for 6-9 months, repeated FNAC may be used for follow-up examination of patients with penile carcinoma.[115]

The diagnostic yield of US can be improved by the addition of FNAC.[116,117] Nevertheless, in two recent studies of US and FNAC in penile cancer, only metastases >2 mm in size were detected and the investigators reported high false-negative rates with the technique.[118,119] In patients with palpable inguinal nodes US with FNAC is the easiest and least invasive way to confirm lymph node metastases, but it is only helpful if positive, as false-negative rates of up to 29% have been reported (LE 3).[5,64,120,121] If FNAC is negative, another aspiration is recommended after a short delay. If negative again and in the presence of clinical suspicion, an excision biopsy is advised.[64]

A prospective study using DSLNB and US-guid-

ed FNAC reported on 64 patients with stage T1 (or greater) cN0 SCC of the penis. The sensitivity and specificity of US was 74% and 77%, respectively. The PPV and NPV were 37% and 94%, respectively. Two patients had a negative initial SLNB; however, US identified a metastatic node and re-evaluation of the SLN confirmed micrometastases. The combination of DSLNB and groin US, with or without FNAC, identified accurately those with occult nodal metastases (LE 3). The authors concluded that US alone is not adequate as a staging technique, and SLNB alone may miss between 5% and 10% of metastases.[113]

Kroon et al. initially used just lymphoscintigraphy to identify the SLN, and introduced US before SLNB to reduce the number of false-negative results.[104] If US and FNAC confirm bilateral disease, then SLNB may not be necessary and the patient can proceed to bilateral ILND. Kroon et al. used US-guided FNAC prior to DSLNB to correctly identify 9 out of 23 positive inguinal basins (LE 3).[119] They suggested that the number of DSLNB investigations needed could be reduced by 10%.

In a study of 16 men with primary SCC of the penis and palpable inguinal lymphadenopathy, FNAC was analysed for 25 palpable inguinal lymph nodes at the time of penile biopsy. FNAC had a sensitivity of 93% and specificity of 91% in predicting metastatic disease. The authors concluded that FNAC permits early ILND where appropriate, without the need for prolonged antibiotic treatment (LE 3).[122]

- **Computed tomography (CT) and magnetic resonance imaging (MRI)**

CT or MRI is recommended in the presence of palpable inguinal lymph nodes to assess their size, extent and location, and the possibility of involvement of any major blood vessel in the nodal mass (Fig. 5). CT and MRI are also able to detect deep, pelvic and retroperitoneal lymph nodes and more distant metastases.[17,64,123]

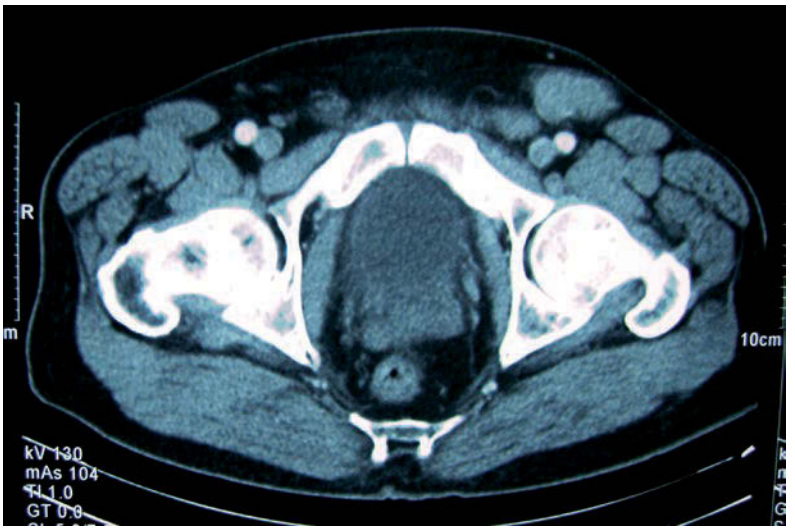

Fig. 5: *CT showing large left inguinal lymph node metastasis.*

In patients with non-palpable nodes, the capacity of CT and MRI to detect lymph node metastases is limited because the diagnosis is based on lymph node size, so micrometastases in normal-sized lymph nodes will go undetected, whereas enlarged nodes secondary to infection or inflammation will be labeled as malignant.[10,17,64,124]

- **Positron emission tomography (PET) CT**

Positron emission tomography (PET) imaging using 18F-fluorodeoxyglucose (18F-FDG) has a high sensitivity and specificity for detecting metastases and disease recurrence in a variety

of malignancies.[113,125] PET in isolation provides only limited anatomical detail, therefore combined PET/CT is used to correlate functional and morphological information.

In a study of 13 patients with suspected penile cancer or suspected recurrent disease 18F-FDG PET/CT had a sensitivity in the detection of primary lesions of 75% (6/8), with a specificity of 75% (3/4). On a per-patient basis, sensitivity in the detection of lymph node metastases was 80% (4/5), and specificity was 100% (8/8). On a nodal-group basis, PET/CT showed a sensitivity of 89% (8/9) in the detection of metastases in the superficial inguinal lymph node basins and a sensitivity of 100% (7/7) in the deep inguinal and pelvic lymph node basins (LE 3).[126,127]

A further study of PET/CT in 20 patients with penile cancer proved that this malignancay is amenable to PET/CT imaging, but the inability to detect microscopic metastases limited its use as a staging modality (LE 3). The spatial resolution of (PET)/CT is limited to several millimetres, so it can not reliably detect micro-metastases (<2 mm).[64]

An evaluation of 18F-FDG PET/CT to detect occult metastases in 24 patients with 42 cN0 groins showed a specificity of 92%, but sensitivity of only 20%, with a PPV of 25% and NPV of 89%. The authors concluded that the role of PET/CT in evaluating the groins of patients with cN0 penile cancer appears to be limited, due to its low sensitivity (LE 3).[128]

The radiation dose from PET or PET–CT is high compared with that from DSLNB, and the availability of PET systems remains limited.[113]

Since MRI is highly accurate for staging of both primary penile cancer and its lymph node metastasis, it may turn out to be the most useful single modality in the staging of penile cancer.[125]

- **Lymphotropic nanoparticle enhanced MRI**

The recently introduced technique of lymphotrophic nanoparticle–enhanced MRI (LNMRI) allows the characterization of lymph nodes in patients with various cancers. Ferumoxtran-10 consists of ultrasmall superparamagnetic iron oxide particles. Normal lymph nodes contain macrophages, which engulf the iron oxide nanoparticles. Malignant lymph nodes lack these phagocytic cells. Therefore, nonmetastatic lymph nodes show homogeneous uptake of ferumoxtran-10 and appear dark on T2-weighted MRI, whereas malignant lymph nodes do not take up the contrast material and appear bright. Because the interpretation is based on nodal function rather than structure, it is possible to detect subcentimeter metastases.[17] The technique involves MRI before and 24 hours after intravenous administration of the nanoparticles.[113,129]

In a study of 77 patients with various malignancies (including 4 penile cancers) LNMRI was compared with surgical lymph node dissection. There was a statistically significant difference in the findings reported by two reviewers, one of whom was more experienced in interpreting ferumoxtran-10-enhanced images, indicating that a certain level of interpretation experience may be required.[130]

Tabatabaei et al. evaluated LNMRI in 7 patients with penile cancer and found a sensitivity of 100%, specificity of 97% and NPV of 100% (LE 3).[129] However, the spatial resolution of both LNMRI and PET/CT are limited to several millimetres, so these modalities can not reliably detect micro-metastases (<2 mm).[64]

- **Gallium-67 radionuclide scanning and fluorescence imaging**

An early study in 6 patients with metastatic carcinoma of the penis evaluated Ga-67 citrate scanning. Intense radioactive uptake was noted in the metastatic inguinal lymph nodes that was not influenced by the presence or absence of infection. The authors suggested that further experience is needed to establish its precise role (LE 3).[131]

A recent study made use of a novel fluorescence assay to attempt detection of tumor-containing lymph nodes.[132] Patients were administered 5-aminolevulinic acid, which was converted into fluorescent protoporphyrin IX preferentially by tumors. The study evaluated 5 patients with clinical lymphadenopathy. Fluorescence of lymph

nodes was evaluated intraoperatively (visually or using a charge-coupled device camera) and compared to preoperative MRI and DSLNB. All three modalities detected what proved to be metastatic disease in two of the patients. The authors recommended further evaluation and dose titration in a larger cohort of patients (LE 3).[16]

Pelvic (iliac) nodes – imaging and surgical staging

Pelvic lymph node metastasis (LNM) is a strong predictor of dismal outcome. In a study of 102 patients the 5-year survival rate for patients with positive pelvic lymph nodes was 0.[57] However, patients with microscopic pelvic LNM may benefit from early pelvic lymph node dissection (PLND). Lopes et al. reported 5 patients with only 1 iliac LNM who exhibited long survival (LE 3).[25] By the time pelvic LNM is detectable on CT, curative surgery frequently is no longer possible. Radiographically visible pelvic LNM warrants a multidisciplinary therapeutic approach (chemotherapy plus surgery).

A study of 73 patients who underwent bilateral ILND revealed that of those with inguinal node metastases, 48.5% had pelvic node metastases. A tumor-positive Cloquet's node indicated an 88.9% risk of pelvic LNM. In patients with negative pelvic CT scan, metastatic involvement of Cloquet's node had a sensitivity of 30.0%, specificity of 94.1%, PPV of 75.0%, and NPV of 66.7%. The incidence of pelvic LNM was 87.5% in patients with 3 or more inguinal LNMs, but only 11.8% in those with 1 or 2 inguinal LNMs. Prognostic factors for pelvic LNM included the number of positive inguinal nodes, the lymph node ratio (number of positive lymph nodes/total number removed), extranodal extension, the expression of p53, more than 3 enlarged inguinal nodes on preoperative CT imaging, and lymph node size = 3.5 cm in long diameter. The authors concluded that the pathological characteristics of the inguinal lymph nodes remain the essential indicators of pelvic LNM (LE 3).[133]

A study of 24 patients with 1 or more positive inguinal lymph nodes showed that the medial inguinal and external iliac lymph node packages were the most commonly involved regions. No extended lymph node metastasis was observed in the absence of positive lymph nodes in the medial inguinal package. Extranodal extension was a significant predictor of extended lymph node metastasis. Cloquet's node was associated with iliac lymph node metastasis on univariate analysis, but it was of limited predictive value in patients with 1 or 2 positive inguinal lymph nodes (LE 3).[134]

In a single-institution study of 100 consecutive patients, managed according to current EAU guidelines, PLND was positive in only 17% of men, underlining the need for stronger prognostic indicators to improve case selection (LE 3).[44]

A study of whole-body 18F-FDG-PET/CT for the detection of pelvic LNM performed in 18 patients with penile SCC showed a sensitivity of 91%, specificity of 100%, diagnostic accuracy of 96%, PPV of 100%, and NPV of 94%. Additionally, PET/CT scans showed distant metastases in five patients (LE 3).[135]

Clearly, the risk of pelvic (iliac) node metastases correlates with the grade and stage of the primary, and especially with the number and histological grade of inguinal node metastases. Pelvic node metastases are extremely unlikely in the absence of inguinal node metastases. It is unclear as to which patients would benefit from pelvic lymphadenectomy, which may be curative in a small number of men with a single iliac node metastasis.

In patients with proven positive inguinal node metastasis, abdomino-pelvic CT scanning is used for identification of pelvic and/or retroperitoneal nodes. A chest radiograph should also be performed in patients with positive lymph nodes. Radionuclide bone scanning is recommended only in symptomatic cases.

Distant metastases

Distant metastases are uncommon in patients who present with penile cancer (<3%-5% of cases) and these are generally accompanied by regional lymph node involvement.[129,136] Generally, hematogenic metastases occur late in the course of the disease and are associated with a dismal prognosis (Figs. 6-7).[56,64,137]

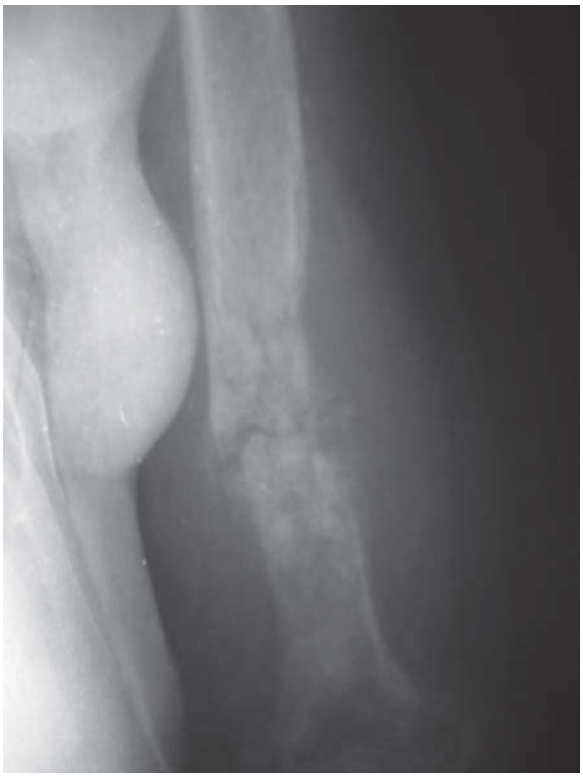

Fig. 6: *X-ray showing metastasis to the left humerus from squamous cell carcinoma of the penis.*

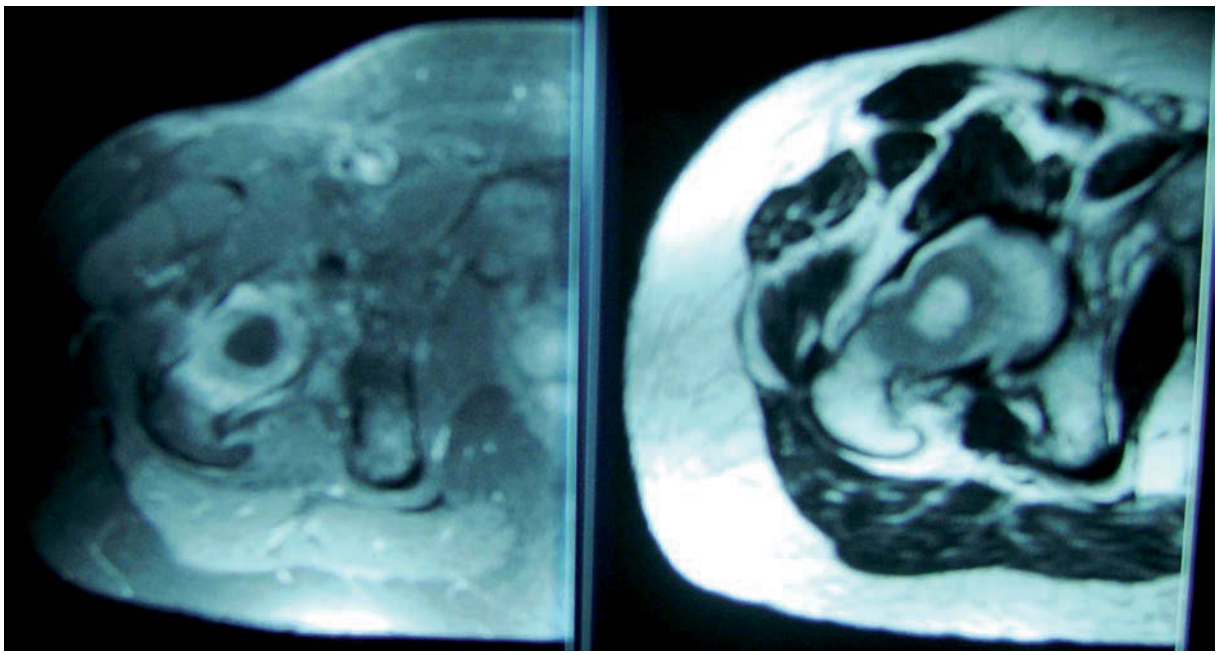

Fig. 7: *MRI showing metastasis to the right femur from penile cancer.*

The most common sites of metastases are the lung, liver, and retroperitoneum.[17] A recent autopsy study of 14 patients with penile cancer, 9 of whom died from disseminated disease, showed the following metastatic sites: lymph nodes (9 cases), liver (7), lungs (6), heart (5), adrenals, bone and skin (3 each), thyroid and brain (2 each), and pancreas, spleen, and pleura (1 each). The authors suggested that the natural history of penile cancer dissemination is: local intrapenile, regional and systemic nodes, regional skin, liver, lungs, heart, and other multiple sites (LE 3).[138]

Case reports include the following unusual patterns of distant dissemination:

- synchronous metastases to the inguinal nodes, liver, lung, skin of the anterior chest wall, and ribs[139]
- pathological fracture of the humerus with hypercalcemia of malignancy[140]
- the kidney, adrenal gland, retroperitoneal lymph nodes, lung, and brain[137]
- bilateral inguinal lymphadenopathy and widespread cutaneous dissemination.[141]

Although CT plays only a limited role in primary tumor evaluation, its use is favored in the evaluation of distant metastases.[17]

Recommendations

1. Physical examination of the primary tumor is mandatory, recording morphological and physical characteristics of the lesion (GR A).
2. Evaluation of the penile lesion with ultrasound (US) is of limited value for local tumor staging (GR C).
3. Evaluation of the primary lesion with magnetic resonance imaging (MRI) during artificial erection induced by intracavernosal injection of prostaglandin may be useful for tumor staging (GR B).
4. Histological or cytological diagnosis of the primary lesion is mandatory (GR A).
5. For accurate histological grading and pathological staging, a resected specimen is preferable, rather than a biopsy alone (GR B).
6. Penile cancer should be staged according to the Tumor, Nodes, Metastases (TNM) system; however, the 1987/2002 TNM staging system for penile cancer does not appear to provide adequate stratification of disease outcome, and requires revision based on data from larger patient cohorts to validate the recently proposed modifications (GR B).
7. The histopathology report should provide information on all parameters that may have prognostic value, including the size of the tumor, histological type, grade, pattern of growth, depth of invasion, tumor thickness, resection margins, lymphovascular and perineural invasion (GR B).
8. Physical examination of the inguinal and pelvic areas to determine the presence of palpable lymph nodes is mandatory (GR B).
9. US-guided fine-needle aspiration cytology (FNAC) is indicated for both palpable and non-palpable inguinal nodes; if it confirms lymph node metastasis, complete inguinal lymph node dissection (ILND) is indicated (GR B).
10. In patients with non-palpable inguinal nodes, if US-guided FNAC is tumor-negative, dynamic sentinel lymph node biopsy (DSLNB) can be performed if the equipment and technical expertise are available (GR C).
11. In patients at high risk of inguinal node metastases according to the available guidelines and nomograms, surgical staging can be performed by complete, bilateral ILND, which may also be curative (GR B).

12. In patients at intermediate risk of inguinal node metastases, sentinel lymph node biopsy (SLNB) or modified (limited) ILND may be performed if DSLNB is not feasible (GR B).
13. In patients with non-palpable inguinal nodes, imaging with computed tomography (CT) or MRI is not useful in detecting large volume lymph node metastases (GR B).
14. Imaging with positron emission tomography (PET) CT and lymphotropic nanoparticle enhanced MRI (LNMRI) to detect small lymph node metastases requires further investigation (GR B).
15. In patients with confirmed inguinal lymph node metastases, CT of the pelvis and abdomen is indicated (GR B).
16. An abdominal CT scan and chest X-ray are advisable if pelvic CT scan is positive (GR B).
17. A bone scan is advisable in patients with symptoms suggestive of skeletal metastases (GR C).
18. Biological laboratory determinations for penile cancer are investigational (GR C).

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Committee 5

New Developments in the Treatment of Localized Penile Cancer

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New Developments in the Treatment of Localized Penile Cancer

E. Solsona (Spain)

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Background

Conventional surgical treatment for invasive penile carcinoma has entailed partial or radical penectomy. Both achieve good local control. However these procedures are associated with significant psychosexual morbidity. Amputative surgery has been based on traditional teaching that a 2 cm macroscopic margin is necessary for adequate surgical control. This figure is not supported by firm evidence and has been challenged by several groups. Recent data have suggested that margins of only a few millimetres may be adequate for most tumors.[1-5]

Hoffman et al. examined pathological resection margins of patients undergoing partial or total penectomy and found no local recurrences in any of their 14 patients, despite 7 having resection margins <10 mm. Average follow-up was 33 months for patients who had partial penectomy and 40 months for the total penectomy group.[2]

Minhas et al. studied resection margins in 51 patients with penile squamous cell carcinoma (SCC) treated with a variety of techniques. Margins measured within 10 mm of the tumor edge and within a <20 mm margin. Their recurrence rate was 4% over a median follow up of 26 months and they concluded that resection margins of a few millimeters may be sufficient to offer adequate oncological control (LE 2b).[3]

In Western countries, the proportion of patients with disease confined to the glans and/or prepuce is around 80%. Interest has therefore been in organ preserving procedures with or without reconstruction. In fact, the percentage of patients undergoing penis preserving procedures is increasing, with more patients undergoing these procedures than penectomy. In contrast, in countries like Brazil the proportion is the opposite, probably due to different demography and sociocultural background (Table 1) (LE 3).

Table 1: Penectomy versus conservative treatment and pathological characteristics of patients with penile carcinoma from Europe and Brazil

Parameters	Ornellas et al.[6]	Mistry et al.[7]	Leijte et al.[8]	Persson et al.[9]
Patients (n)	688	72	700	454
Penectomy (%)	61	40	40.6	37.9
Conservative procedures (%)	39	60	59.6	62.1
Tis-Ta (%)	-	11.4	13.7	32
T1 (%)	13.5	47.5	32.5	24
T2 (%)	47	21.3	41.3	28
T3 (%)	25.6	1.6	6.4	6
T4 (%)	6.2	-	0.6	3
Tx (%)	7.7	1.6	5.6	3

Methodology

The incidence of penile carcinoma is very low, there are no randomized trials available comparing penectomy and penile preserving approaches, the vast majority are retrospective or small prospective case series and the wide range of penile preserving approaches makes it impossible to obtain a high level of evidence. In our literature review the level of evidence ranges from 2a to 4, mostly 3.

The literature has been peer reviewed since 2000, although important series not updated and published before 2000 were also included and classified according to the Level of Evidence (LE). Review articles and others indirectly related to the topic have also been included in the text but not classified. In summary, 67 articles constitute our peer literature review, being classified and allocated according to procedures and quality of life, although some of them have been repeated as shown in Table 2.

Table 2: Articles allocated and classified following level of evidence and according to procedures and quality of life

Procedures	No. articles*	LE 2a	LE 2b	LE 3	LE 4
Partial / total penectomy	10	-	2	10	-
Laser treatment	7 (1)**	-	1	6	-
Conservative approaches	13	-	1	13	1
Radiotherapy	10 (4)**	-	-	10	-
Penile reconstruction after penectomy	8	-	-	7	1
Quality of life	20 (7)**	-	-	14	3
Global evaluation	6	-	-	5	1

LE: level of evidence; * some articles were included in more than one item and sometimes provided different levels of evidence for different procedures; ** articles before 2000

This chapter firstly discribes the different treatment procedures, analysing the global results, potential indications, complications and their advantages and pitfalls. Secondly, an analysis was made about local recurrence as a main oncological end point. Thirdly, a specific section was devoted to penile reconstructive surgery after penile amputation, as there is an increasing social demand for penile preservation from these patients. Fourthly, quality of life was included as an important issue in the therapeutic decision making process. Finally, consensus recommendations for treatment of the primary tumor reached by members of the subcommittee were summarized.

PROCEDURES

1. Amputative surgery: partial / total penectomy / emasculation

Partial penectomy

Partial penectomy for SCC of the penis provides excellent local control, with low recurrence rate, and acceptable maintenance of urinary and sexual function (Figs. 1-2).[10] Invasive tumors involving the glans and coronal sulcus can be adequately managed by partial penile amputation excising around 1.5 to 2.0 cm of normal tissue proximal to the margin of tumor infiltration. In most instances, this should leave a functional penis of over 4 cm in length, which allows standing micturition, and enough rigidity and length for vaginal penetration. Frozen sections of the proximal margins are necessary to confirm tumor-free resection and a recurrence rate of less than 10% is expected.

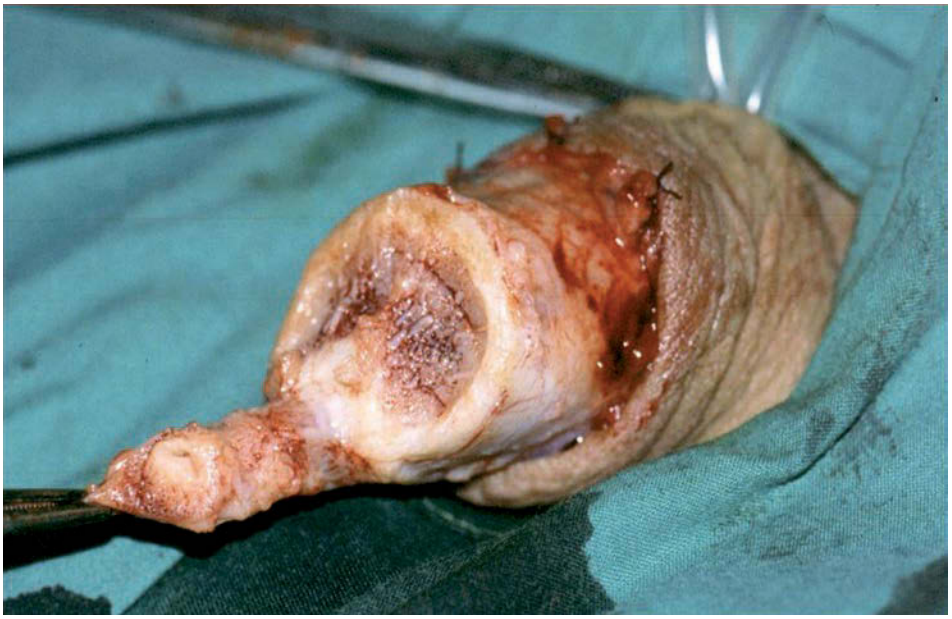

Fig. 1: *Partial penectomy - resection of corpora cavernosa and urethral stump.*

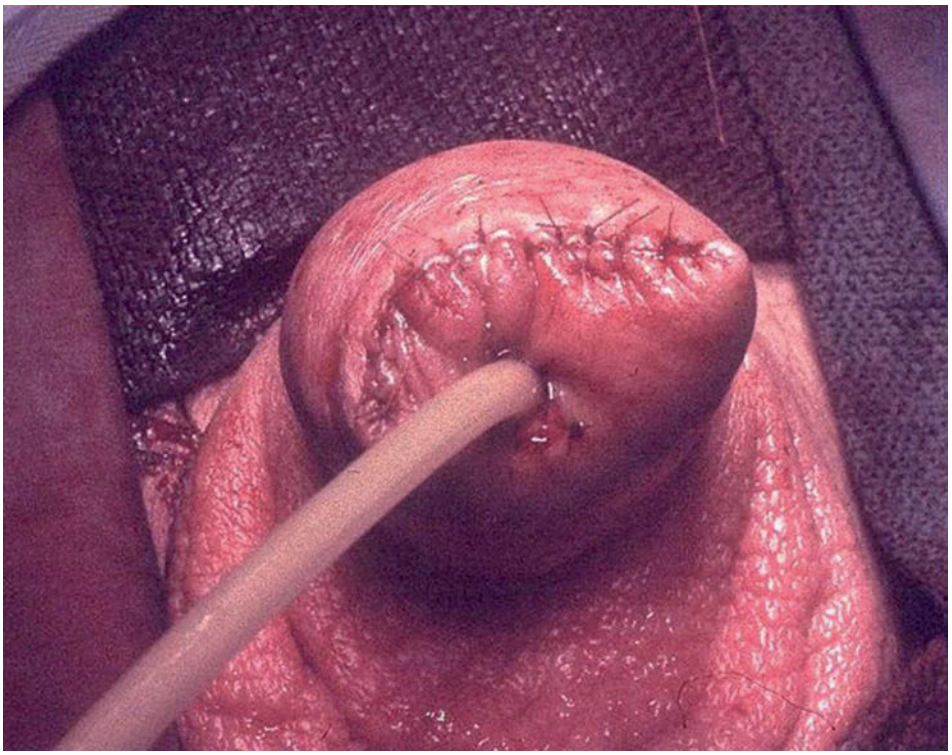

Fig. 2: *Partial penectomy - completed.*

The procedure can be performed under local, regional or general anesthesia. The lesion and urine should be cultured preoperatively and appropriate parenteral antibiotics started prior to the surgical procedure. The penis is prepped with povidone/iodine solution and the tumor isolated using a sterile condom/glove that is sutured in place. A 0.25 inch Penrose or 14F Red Robinson catheter is applied as a tourniquet at the base of the penis. An angled incision is marked on the skin 1.5 to 2.0 cm proximal to the lesion. The skin is incised and the superficial and deep dorsal veins divided and ligated. Buck's fascia is incised onto the tunica albuginea of the corpora. The corpora

cavernosa are sharply divided down to the urethra and the central cavernosal arteries ligated on each side.

The urethra is dissected free from the corpus spongiosum in such a manner that an approximately 1.0 cm stump projects distally to the transected corpora cavernosa. The urethral stump and transected corpora are then washed with gentamycin solution. The corporal ends are closed with horizontal mattress sutures of 2.0 Vicryl incorporating Buck's fascia, tunica albuginea, and intercavernous septum. The penile base tourniquet is then released and all minor vessels are fulgurated or ligated until adequate hemostasis is obtained.

Skin closure can be performed either in the classic longitudinal fashion or using a button-hole technique in which a flap of dorsal penile skin is left, a crescentic button-hole incision in the skin flap is made and this flap is then rotated ventrally toward the urethra. In both techniques the urethra is spatulated dorsally and sutured to the skin using 4.0 absorbable sutures. The remaining skin is closed using 3.0 absorbable sutures. A 16F Foley catheter is left indwelling to closed straight drainage for 48 hours and the wound is dressed with triple antibiotic and vaselinated gauze.[11]

Total penectomy

Patients with large, extensive, and infiltrating lesions involving the glans and midshaft of the penis, in which the location precludes adequate excision with a functional residual penile remnant are managed by total penectomy. The patient is placed in the lithotomy position and the lesion is prepped in the same way as in partial penectomy.[11] An elliptical incision is made around the base of the penis and extended through the subcutaneous tissues until the surface of the pubis is reached. All vessels and lymphatics are either fulgurated or ligated. The suspensory ligaments of the penis are isolated with a right-angle clamp and divided. The dorsal vein and penile arteries are identified, clamped, ligated, and divided.

The penis is then reflected cephalad, Buck's fascia is opened ventrally, and the urethra is dissected free from the corpora cavernosa with sharp and blunt dissection. At the distal bulbar region, the urethra is divided, leaving enough length to reach the perineum. The corpora cavernosa are dissected up to the ischiopubic rami, sutured, and ligated with 2.0 absorbable sutures and then transected. The specimen should be removed with a 2.0 cm tumor-free margin.

The urethra is then dissected to the area of the urogenital diaphragm to obtain an un-angulated straight course to the perineal urethrostomy site. A 1.0 cm ellipse of skin and subcutaneous tissues are removed from the mid-perineum just midway between the anus and scrotum. A tunnel is developed in the perineal subcutaneous tissue using a curved clamp and the urethra is drawn into the perineal incision with care to avoid angulations in the urethra. The urethra is then spatulated dorsally and a V-inlay of skin can be created and anastomosed to the skin using 3.0 or 4.0 absorbable sutures. A watertight technique should be used to prevent urinary leakage under the flap. An 18F Foley catheter is inserted and 0.25 inch Penrose drains are left to drain each side of the scrotum.

The scrotal incision is closed transversally to allow elevation of the scrotum away from the perineal urethrostomy using a two-layered closure. Triple antibiotic is placed over the wound incision and around the perineal urethrostomy. A vaselinated gauze, pressure dressing and scrotal support are applied for 24 hours. The Penrose drains are usually removed in 48 hours and the Foley catheter should be removed when the urethrostomy is well healed.

Perineal urethrostomy is indicated when total penectomy is performed or when the penile stump does not allow upright micturition. Probably, in this situation total penectomy should be offered to these patients if penile reconstruction is not accepted.

Lesions involving the perineum and anterior abdominal wall may need adjuvant preoperative chemotherapy in an attempt to downsize the tumor. If no adequate response is observed, the patient will need complete removal of the neoplasm which may result in total emasculation and may require a musculocutaneous flap closure.[12]

In some rare instances cystoprostatectomy with urinary diversion will be necessary.

Complications

The most common complication of partial or total penectomy is meatal stenosis (3.5%-9%).[10,13] The V-inlay technique has been used to decrease the risk of stenosis at the urethral opening.[11] Some institutions also advocate the use of a "loop" cutaneous urethrostomy, instead of the classic end cutaneous urethrostomy, during total penectomy which may better preserve the distal urethral blood supply and thus minimize the tendency for the urethral meatus to develop stenosis. Patients should be aware of this complication and instructed to start self-dilation as soon as they notice a decrease in the urine stream.

Patients with partial or total penectomy suffer serious psychological and physical trauma with major changes in their quality of life. Some authors have proposed that the classic 2.0 cm excision margin is not necessary and a more conservative approach might still offer adequate cancer control while providing a more cosmetic and functional penile remnant.[3]

Technical modifications.

Attempting to retain as much penile length as possible using frozen sections of the corporal tips in order to establish negative surgical margins less than 2 cm and using a split- or full-thickness skin graft a neo-glans can be created.[14] Furthermore, a technique to improve glans sensitivity has been developed using the spatulated distal urethra to cover the exposed corporeal tips.[15] Partial amputation, done by performing a hemispherical incision of the corpora cavernosa, thereby creating a dome-shaped stump to which the skin graft is applied, can improve the cosmetic results.[16]

2. Penile preserving strategies: surgical options

T1 lesions limited to the foreskin

Wide **local excision** with circumcision is sufficient primary curative therapy for low-stage disease.[17,18] Adequate clearance margins must be achieved. For more proximal lesions, circumcision margins may have to be extended to the shaft of the penis to ensure adequate clearance.[19,20] In cases of highly suspicious lesions, 5% acetic acid may be used to demonstrate all abnormal areas.[14] A swab soaked in the solution is applied to the penis for 2-3 minutes. This stains areas of otherwise undetectable penile intraepithelial neoplasia (PIN) white, thus guiding the margins of excision.

T1 lesions of the glans

If the lesion involves the glans, a **partial glansectomy** may be performed (Figs. 3-4). Large defects caused by such excisions may need partial thickness or full-thickness skin grafting, however, some will only require primary closure. In instances of co-existing glans carcinoma *in situ* (CIS), **topical chemotherapy** with 5% 5-fluorouracil (5FU) cream or 5% imiquimod cream during 6-8 weeks can be used to control the CIS in first or second line with a success rate of 70% and 52% respectively.[21] Close follow-up is imperative.

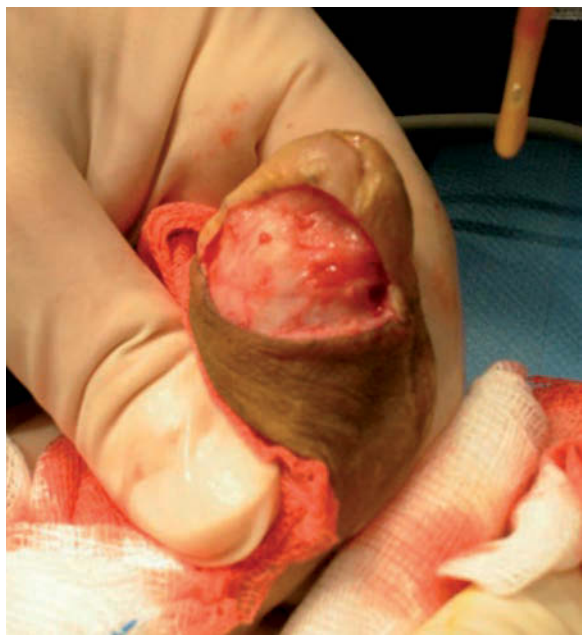

Fig. 3: *Partial glansectomy.*

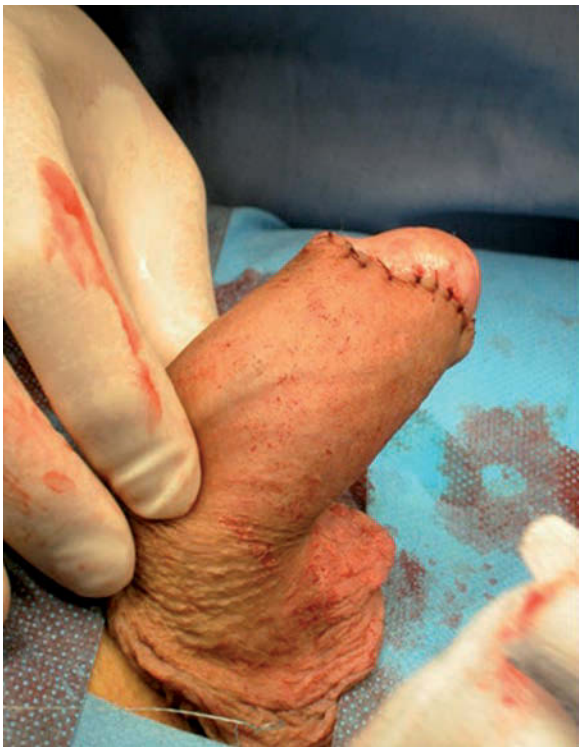

Fig. 4: *Partial glansectomy - completed.*

Another alternative is to perform **glans resurfacing** i.e. removing the glans skin from 1 cm. beyond the coronal sulcus to the urethral meatus in quadrants and resurfacing with split- or full-thickness skin graft (Figs. 5-7).[22]

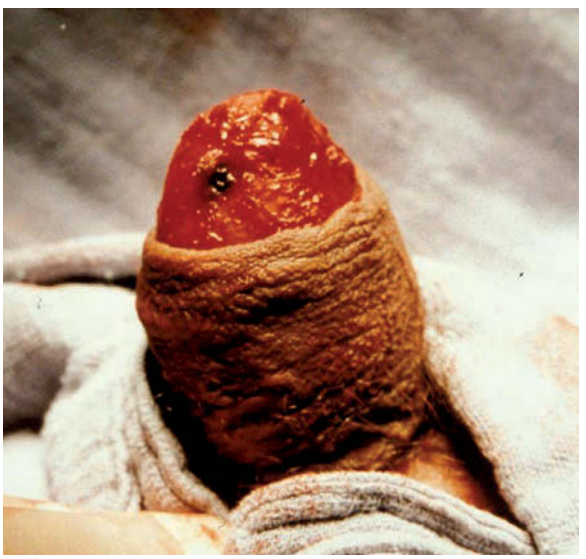

Fig. 5: *Glans resurfacing - removing the glans skin.*

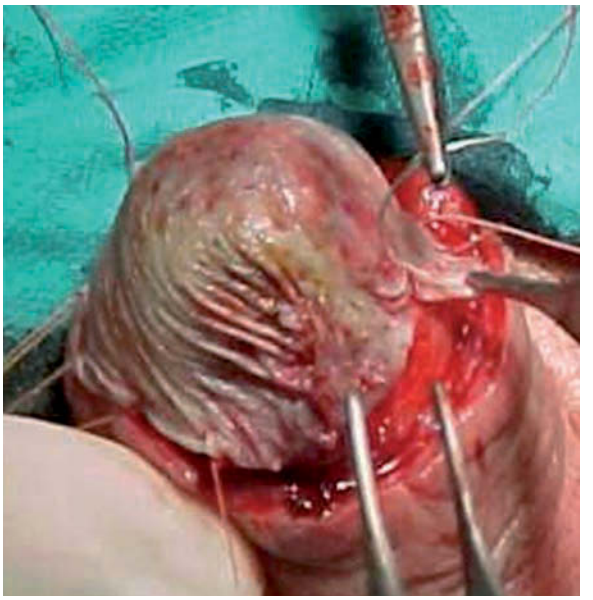

Fig. 6: *Glans resurfacing – split-thickness skin grafting.*

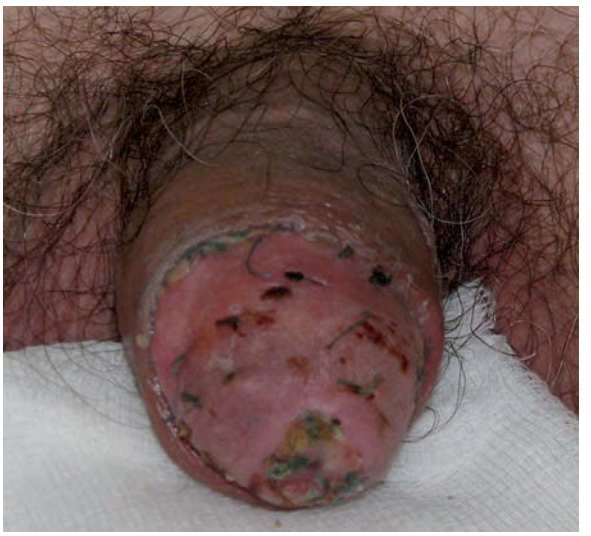

Fig. 7: *Glans resurfacing – postoperative appearance.*

Laser treatment has most commonly been described for the treatment of CIS, however some groups have also used the technique for the treatment of invasive disease.[23-27] Carbon dioxide laser has a penetration of 2-2.5 mm and it can be delivered with an output of 15-20W. A focused beam is used in place of a scalpel to excise tumor, thus obtaining a histological specimen, whilst Neodymium:YAG laser has a penetration of 3-5 mm, with an output of 24-60W, and can be

used to destroy tumors by coagulation. The latter technique does not produce a histological specimen and therefore has the potential to understage tumors.

An early series of 47 men who were treated with carbon dioxide laser for very superficial disease (mean depth of 1.5 mm) suggested good disease control.[24] However, in a more recent series of 67 men treated with combined carbon dioxide and neodymium:YAG laser, 13 patients (19%) had disease recurrence, including 3 with multiple recurrences. In 3 patients the recurrence was of a higher grade and/or stage than the original tumor.[25]

Complications range from 1% to 7% and include minor post-operative bleeding,[25] moderate pain and preputial lymphoedema in some patients.[28,29] No meatal stenosis or impaired voiding was noted in one series.[26] The long healing period is a disadvantage of this procedure, and in extremely obese patients the phallus is buried in the pubic fat. Cosmetic results as well as voiding function are usually excellent.[25,26,29]

Mohs microsurgery is a technique of excision of the lesion in thin horizontal layers using microscopic examination of the entire undersurface of each layer and systematic use of frozen sections.[30] Two techniques have been described by which microscopic control of the tumor is achieved. The first technique is a fixed tissue technique in which the tissues are subjected to *in situ* chemical fixation with zinc chloride paste before excision of successive layers. In the fresh tissue technique, a local anaesthetic is injected and the tissues excised in fresh, unfixed state and examined by frozen section. The fresh tissue technique is recommended for small tumors, whereas for larger infiltrative lesions the fixed technique will provide control of bleeding from the relatively non-contractile vessels of the erectile tissues of the glans and corpora cavernosa.

Complications range from 1.2% to 3.6%, and include wound dehiscence, meatal stenosis and remnant urethral disease.[31] The advantages include maximal preservation of normal uninvolved tissue, the procedure is highly effective, well tolerated, and has low post-operative risk. Disadvantages include the potential for a misshapen glans, the need for reconstruction in large tumors, skilful personnel including urologists and pathologists and the time-consuming nature of the technique.

T2 lesions involving the glans

In 1997 Austoni et al. were one of the first groups to emphasize the anatomical distinction between the corpora cavernosa and corpus spongiosum and propose glansectomy as an effective treatment for glans confined penile cancer.[32] **Glansectomy** involves the dissection of the glans penis from the corpora cavernosa (Figs. 8-10). A circumferential incision is made in the distal shaft skin down to Buck's fascia, and a plane of dissection is developed between the glans and corporal tips.

The urethra is mobilised to allow the meatus to be at the tip of the penis. In some series the exposed corporal tips are covered with a partial thickness skin graft.[4,14,16,33] The graft is quilted to the corpora to prevent haematoma formation beneath it. Frozen section analysis of resection margins is advisable to ensure complete resection of the tumor. Given the observed spreading pattern of penile tumors,[5] Algaba et al. suggested that tissue from the urethral and corporal margins would be most useful.[34]

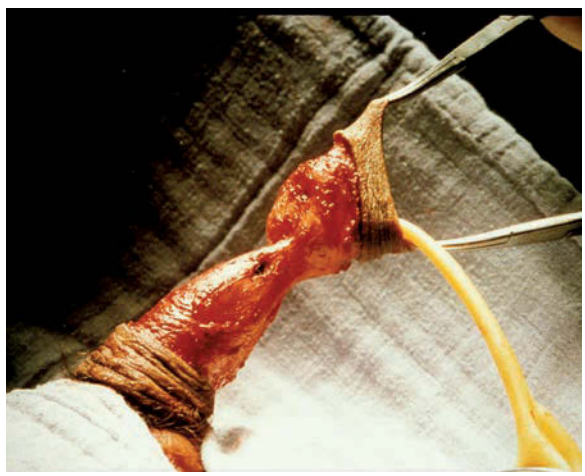

Fig. 8: *Total glansectomy.*

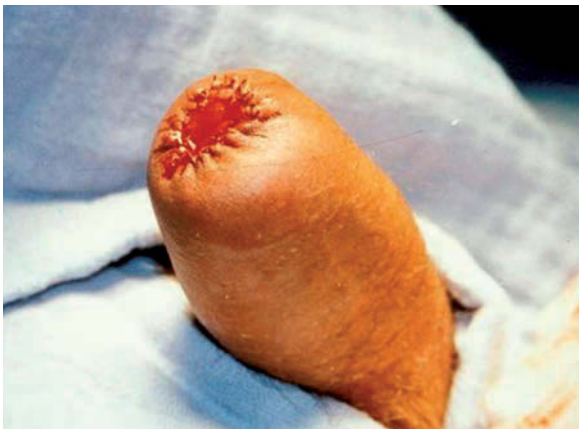

Fig. 9: *Total glansectomy - skin flap advancement.*

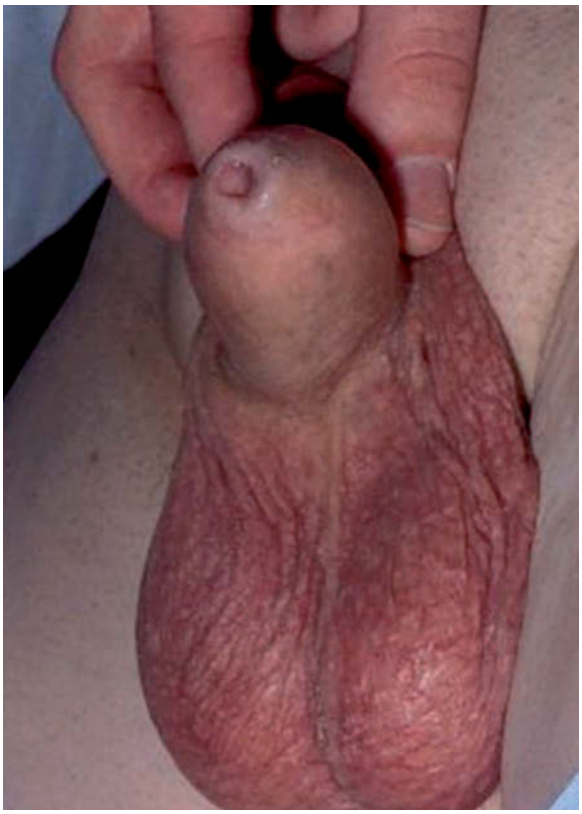

Fig. 10: *Total glansectomy with skin flap advancement - postoperative appearance.*

Davis et al. described 3 patients who had undergone glansectomy for the treatment of verrucous carcinoma, angiosarcoma and malignant melanoma.[35] There was no local recurrence in any of these patients, although the patient with angiosarcoma did develop distant metastasis. The paper of Hatzichristou et al. described 7 patients with Buschke-Löwenstein tumors who were treated with glansectomy without skin graft reconstruction. One patient developed local recurrence at 3 months and was successfully treated by partial penectomy. All patients were disease-free at 18 to 65 months follow-up with acceptable aesthetic results and expressed satisfaction with their sex lives.[36]

Bissada et al. reported on 30 patients who were treated with "unconventional tailored surgical excisions". This paper did not describe the surgical techniques other than to say that it entailed "complete primary excision of the tumor with preservation of uninvolved penile structures". Over a follow up of 12-360 months, 21 patients were disease-free, and 3 patients had local recurrences which were successfully treated with further resection. One patient had died of disease.[18]

Pietrzak et al. described 1 local recurrence in a patient who had undergone partial glansectomy, but not in any patient who had undergone total glans excision. This was felt to be due to tumor growth in surrounding unstable epithelium.[14] In the largest series to date, the same team described 3 local recurrences in patients who had been treated by glansectomy with an overall recurrence rate of 4%.[4] This figure is comparable to the recurrence rates after a 'standard' partial penectomy.[10]

The urethra can be used (negative frozen section) by everting the urethral mucosa to cover the corporal tips, the shaft skin is sutured closely to it and no skin graft is required.[37] Another technical modification is described where the whole urethra is fully dissected and mobilized from the anterior corpora cavernosa, the ventral part of the urethra is longitudinally opened for 3 cm and shaped to cover the corporal tips, in the same fashion as in partial penectomy, and no split-thickness graft is necessary.[15]

Distal urethral SCC

Glanular urethral tumors are most commonly SCCs and their behaviour is similar to penile carcinoma. Glans preserving surgery has been described, although due to the rarity of the condition case series are small.[15,38]

Complications

Partial graft loss, graft contraction, graft overgrowth of the external urethral meatus, and partial dehiscence of the neoglans are the most common complications.[4,14] Revisional surgery for positive margins can be performed when they are found in pathological examination. Urethral stenosis is another possible complication, although less commonly reported than for partial penectomy.[18] In general the incidence is very low (1.3%-14%), and some authors reported no complications.[16,22]

One problem of these techniques is the glans sensitivity reduction, although this can be improved using graft reconstruction or urethral mucosa to cover the corporal tips.[15,22] Spraying urine when voiding is another problem, but preserving the whole urethra also improves standing-up micturition. Donor-site morbidity in cases of grafting is a pitfall for these patients, as well as the prolonged hospital stay. However, the cosmetic results are generally excellent, allowing natural micturition, normal sexual activity and improved self-image.[15,16,22]

Neo-adjuvant chemotherapy and conservative rescue treatment

In specific locally advanced cases induction chemotherapy followed by conservative surgery can be an option within clinical trials. Bandieramonte et al. in a study of 40 patients performed reductive chemotherapy with vincristine, bleomycin and methotrexate before performing laser excision, partial in 3 cases and total surface excision in 37 cases. No residual tumor was observed in 16 patients.[29]

3. Radiotherapy

One of the traditional conservative approaches for local tumor control is radiotherapy with different modalities, such as external radiation therapy (RT) and/or interstitial brachytherapy, which have been used for many years in several institutions to preserve penile function. If RT is chosen, surgery can be reserved for salvage.[39,40]

External beam radiotherapy offers local control rates of about 60%-70%. Parallel-opposed lateral fields with Co^{60} or 4-6 Mv photons are in general used to encompass the entire length of the penis. Doses from 40 to 78 Gy are used (median dose of 60 Gy) and dose per fraction ranges from 1.7 – 3.8 Gy (median dose of 2 Gy). The physical set-up consists of a rectangular wax block placed around the shaft of the penis to achieve a uniform dose distribution according to the Toronto technique.[41] Others have used a cellulose acetate shell made specific for each patient, with unit density beeswax paraffin built up around the shell to increase the dose to the surface and improve the dose homogeneity.[42] General indications include young men with small (i.e. <4 cm), superficial and exophytic lesions, located on the glans or coronal sulcus. Medically unfit patients and those who decline surgery will be other candidates for these procedures. It can also be offered as palliation in patients with metastatic disease.

Brachytherapy

Indications for brachytherapy alone are, in principle, all tumors up to 4 cm, strictly limited to the glans and not extending beyond the balanopreputial sulcus. The target volume (CTV) encompasses the tumor volume (GTV) plus a safety margin of 5-10 mm. Since superinfection is very often associated with cancer of the penis, it is difficult to delineate the exact target volume.[39,43]

The first step in treatment is to perform a wide circumcision, which has two aims: first to allow optimal tumor assessment, and consequently better determination of the target volume; secondly to decrease side-effects of brachytherapy or external beam RT. The target volume must also be defined taking into account the different tumor types: superficial or infiltrating tumors; thickness, peripheral limits, exophytic tumors; accurate knowledge of the tumor and its basis (depth of invasion), exact topography of the infiltration, and depth of the ulceration. The anatomical position of the penile urethra should be marked with a Foley catheter and some authors consider it necessary to include the whole glans in the target volume. Technically there are two main techniques:

Plesiobrachytherapy: It is indicated for very superficial lesions (no more than 5 mm thick) with well defined limits.[44,45] Essentially two types of surface applicators can be used: a personalized one, made for each patient, or a standard one, less individualised but perhaps easier to use. The first consists of a mould containing catheters placed according to the tumor topography afterloaded with an iridium source for HDR (high dose radiation) or LDR (low dose radiation) brachytherapy.

The second is more often used; it is made of two plastic cylinders, the inner one worn over the penis, the outer one containing iridium sources. This kind of LDR brachytherapy requires close compliance from the patient, who usually has to place the applicator around the penis himself and also record the exact duration of each treatment.

Interstitial brachytherapy: The classical procedure is based on the use of hypodermic needles manually afterloaded with iridium wires (Fig. 11).[42,46] The main disadvantages are that this is a protracted and detailed technique, it involves risks of sepsis; parallelism of the needles is not always possible. Gerbaulet's glans applicator (GAG)[39] consists of 2 square plates of transparent plastic, 50 mm wide and 2 mm thick. These two identical plates are perforated by holes, to allow the passage of hypodermic needles; these perforations are located at 5 mm intervals from each other, forming a regular equilateral/ triangular-shaped arrangement which is ideal for a homogeneous distribution of dose according to the Paris System rules.[40] The parallelism of the plates and needles is thus ensured, and is maintained throughout the treatment.

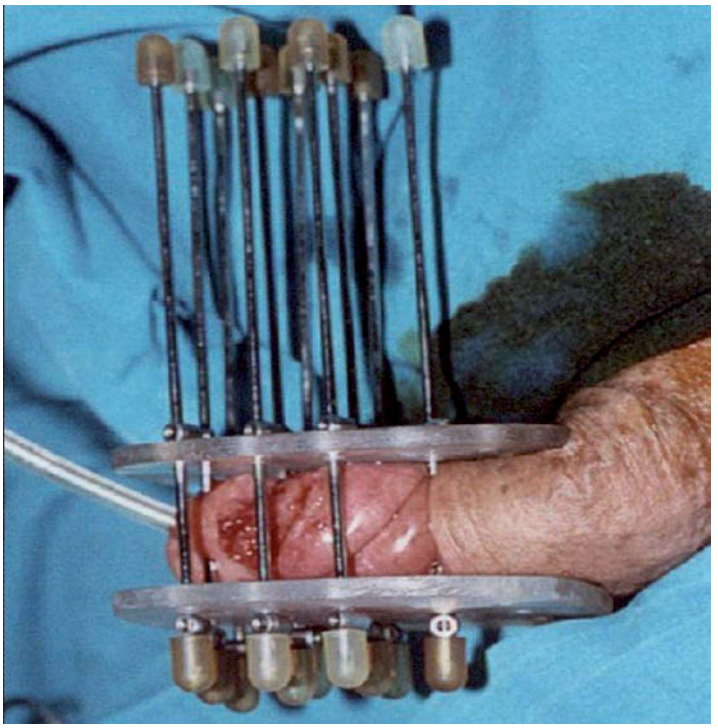

Fig. 11: *Interstitial brachytherapy for penile carcinoma.*

The use of this new technique of implant significantly saves time and improves logistics. The patient's tolerance is greatly increased as the risk of infections is reduced and problems of secondary distortion are eliminated. The whole apparatus is lightweight. Finally, a better quality implant is achieved allowing an increase in local control. The dose to the testis should be as low as possible, and using a sponge to keep the radioactive sources away from the penis is recommended.

Dose, Dose Rate, Fractionation

For LDR plesiobrachytherapy as well as for LDR interstitial brachytherapy the minimal target dose (PTV) is usually 65 Gy delivered in 6-7 days at a dose-rate of 40 Gy per hour. The mean central dose is 75 Gy. The treated volume is dependent on the target volume, mean 50 cc.[47,48] Some authors prefer to deliver brachytherapy at a higher dose rate using a silicone mould, the dose of brachytherapy ranges from 32 to 74 Gy (with or without electron boost), with a median dose rate of 2 Gy/hour.[39,49]

For HDR brachytherapy published data are very scarce. As far as critical organs are concerned, the dose to the urethra should be restricted as much as possible. In any case, direct implantation of the urethra must be avoided.[50] Dose to the urethra and to the testis is calculated routinely. As tumor related infections are frequent in these patients as well as urinary infection, prophylaxis with antibiotics should be advised with routine urine analysis.

Adverse side-effects

Acute side-effects: For plesiobrachytherapy the tolerance during treatment is quite acceptable, since the lesions are superficial and usually not infected.[44,45] For interstitial implants, antibiotic therapy, anti-inflammatory and analgesic treatments should be prescribed. Because of the risk of radioepidermitis and radiomucositis, sometimes complicated by dysuria or urinary infection, it is often necessary to continue this treatment for some weeks following the implant.[43,46,51] Desquamation is another important complication, as sometimes it is very difficult to differentiate it from residual tumor and a biopsy is necessary, increasing the risk of radionecrosis.

Late side-effects: The complication rate is proportional to the total dose, the dose distribution, and the treated volume. Telangiectasia and/or sclerosis are frequent, but do not impact on quality of life. In contrast, urethral stenosis (3%-44%) and/or necrosis (1%-14%) are less frequent, but may have a significant impact on quality of life; in fact from 20% to 39% of these complications require partial penectomy.[39,41,43,46,50,52-54]

LOCAL RECURRENCES

Incidence and rescue therapy: The low incidence of penile cancer and consequently low number of patients undergoing surgical treatment of the primary tumor with low local recurrence rates (20%-25%) result in a very small number of patients scattered over several studies worldwide.[55] Consequently meaningful analysis of the literature is not possible. The evidence presented is extracted from two articles which specifically deal with this topic, 18 articles that reported their management of patients with local recurrence and 3 review articles dealing with this topic. All treatment approaches for primary tumors of the penis have been shown to be effective in controlling the primary tumor, but are at different risk of recurrences during follow-up.

The incidence of local recurrence in patients treated with **partial or total penectomy or emasculation** is very low. In a literature review in the most recent 9 publications on 1490 patients, the recurrence rate was 4%, being 4.6% for patients who underwent partial penectomy and 0.7% for those treated with total penectomy or emasculation (Table 3) (LE 2b). The vast majority of patients initially undergoing partial penectomy can be rescued with total penectomy or emasculation at relapse, or with palliative RT for inoperable patients. Ornellas et al.[6] reported that among 25 patients with local recurrence after partial penectomy, 8 (32%) were rescued with partial penectomy, although 4 of these patients relapsed again and underwent total penectomy or emasculation.

Table 3: Local recurrence after penectomy					
Author	**Penectomy**	**Pts (n)**	**Local recurrence n (%)**	**Rescue therapy (n)**	**Mean FU**
Bañon et al.[56]	Partial	42	3 (7.1)	3 (TP)	67.3 mo
	Total	11	0	-	-
Ficarra et al.[57]	Partial	30	0	-	69.4 mo
	Total	5	0	-	-
Rempelakos et al.[58]	Partial	227	0	-	> 10 yrs
	Total	75	0	-	
Chen et al.[59]	Partial	34	2 (5.8)	-	37 mo
	Total	5	0	-	
Mistry et al.[7]	Partial	18	1 (5.5)	1 (TP)	1993-
	Total	6	2 (33.3)	2 (RT)	2003
Lont et al.[13]	Partial/total	100	10(10)	-	106 mo
Korets et al.[10]	Partial	32	1(3.2)	-	34 mo
Leijte et al.[8]	Partial	214	15 (5.1)	-	60.6 mo
	Total	71	0	-	
Ornellas et al.[6]	Partial	522	25 (4.0)	21 (TP) /4 (PP)	11 mo
	Total	98	0		
TP: total penectomy; PP: partial penectomy; RT: radiotherapy					

Penile preserving surgery: different procedures (local excision, Mohs micrographic surgery and glansectomy) were included in the same group for analysis for a total of 10 articles since 2000. The average recurrence rate was 9.2% (Table 4) (LE 2b) lower than that of older series ranging from 11%-50%.[35,60-62] This decreased recurrence rate is probably due to the improvement in surgical techniques and the systematic incorporation of frozen section biopsies to identify negative surgical margins (LE 2b). One series with no frozen section biopsies included in its surgical technique reported the highest recurrence rate (25%).[56] As many local recurrences after penile preserving surgery are multiple, they are usually re-treated with penile preserving procedures,[14,16,18] and partial penectomy is reserved for more aggressive recurrences.[31]

Laser treatment is well suited for the management of Tis as well as superficial invasive penile carcinoma. A recent literature overview on 7 series established that the recurrence rate was 18.3%, with a tendency to higher recurrence for more locally advanced tumors: 14.2% for Tis and 20.6% for stages T1-3 (Table 5) (LE 3). When frozen section was included in the surgical procedure the recurrence rate dropped to 6.8%[26] compared with a rate of 19% for those using laser coagulation after tumor excision.[25] Many of the recurrences after laser treatment were also multiple[23,26] but were initially controlled with repeated laser treatment. However, some had to be controlled eventually with partial or total penectomy.

Table 4: Local recurrence after penile preserving strategies						
Author	**Procedure**	**Pts**	**Frozen b**	**Local relapse n (%)**	**Rescue therapy**	**Mean FU**
Bañon et al.[56]	Local excision	20	No	5 (25)	1 PPS / 4 PP	67.3 mo
Bissada et al.[18]	Local excision	30	Yes	3 (10)	3 PPS	1-30 yrs
Shindel et al.[31]	Mohs procedure	33	Yes	8/25(32)	MMS / 2 PP	
Gulino et al.[15]	P/T glansectomy no grafting	14	Yes	0		13 mo
Brown et al.[37]	P/T glansectomy no grafting	5	Yes	0		12 mo
McDougal[63]	P/T glansectomy ± resurfacing	7	Yes	2 (28.5)	2 PPS	2-5 yrs
Pietrzak et al.[14]	P/T glansectomy + grafting	39	Yes	1(2.5)	2 PPS	16 mo
Hadway et al.[22]	Glans skinning + resurfacing	10 (Tis)	Yes	0		30 mo
Smith et al.[38]	P/T glansectomy + resurfacing	72	Yes	3 (4)	PPS	27 mo
Palminteri et al.[16]	P/T glansectomy + resurfacing	17	Yes	0	-	32 mo
P/T: partial/total; MMS: Mohs micrographic surgery; Frozen b: frozen section biopsies; PPS: penile preserving surgery; PP: partial penectomy; FU: follow-up						

Table 5: Local recurrence after laser treatment						
Author	**Procedure**	**Pts**	**Frozen b**	**Local relapse (%)**	**Rescue therapy**	**Mean FU**
Tietjen and Malek[28]	CO_2/Nd:YAG	44 (T1-2)	No	5 (11.4)	PPS / 2PP	58 mo
Van Bezooijen et al.[65]	CO_2/Nd:YAG	19 (Tis)	No	5 (26.3)	PPS / 1 PP	32 mo
Frimberger et al.[26]	Nd: YAG	29: 12 (T1-2); 17 (Tis)	Yes	2 (6.8) 2 (17.2) (T1-2) 0 (Tis)	PPS / 1 PP	46.7 mo
Windahl and Andersson[25]	CO_2/Nd:YAG	67: 56 (T1-3) 21 (Tis)	No	13 (19) 10 (21.7) (T1-2) 3(14.2) (Tis)	PPS / 2PP	42 mo
Tewari et al.[27]	Nd:YAG	32	No	2 (6.2)	PPS	70 mo
Meijer et al.[64]	Nd:YAG	44: 38 (T1-2) 6 (Tis)	No	29 (66) 25 (65.7) (T1-2) 4 (66.6) (Tis)	PPS / 20 PP	44 mo
Bandieramonte et al.[29]	CO_2	224: 118 (SCC) 106 (Tis)	Peniscopy	32 (14.2) 12 (11.3)(Tis) 20 (16.9) (T1-2)	PPS /8 PP + 1 TP	66 mo
PP/TP: partial/total penectomy; Frozen b: frozen section; PPS: penile preserving surgery; FU: follow-up						

Radiotherapy

This may seem to offer an ideal combination of cancer control and penile conservation, but penile SCC is a radioresistant tumor and a balance between radiation dosis and tumor control is necessary. In this section, the 5-year local tumor control was evaluated, including residual tumor after treatment and local recurrence during follow-up, which ranged from 55% to 65%, while the 5-year penile preservation rate ranged from 43% to 65% (Table 6) (LE 2b). These figures seem improved up to 70%-85.5% for local control and up to 70%-86.5% for penile preservation at 5 years when patients were treated with interstitial brachytherapy (Table 7) (LE 2b). In general, the vast majority of local relapses after RT required partial or total penectomy. Nevertheless, Smith et al.[4] were able to successfully treat 7 patients with penile preserving surgery after local relapse of RT.

Table 6: Local recurrence after radiotherapy

Author	Method	Pts (n)	Dose (Gy)	5 yr local control (%)	5 yr penile preservation (%)	Mean FU
Sarin et al.[54]	EBRT	59	60	55	50	5.2 yrs
Gotzasde et al.[66]	EBRT	155	40-60	65	65	
Azrif et al.[42]	EBRT	41	50-52	62	62	4.5 yrs
Ozsahin et al.[41]	EBRT	33	52	63	43	14 mo
Rozan et al.[50]	BT	184	63	86	78	139 mo
Soria et al.[68]	BT	102	61-70	77	72	111 mo
Chaudhary et al.[67]	BT	23	50	70	70	21 mo
Kiltie et al.[69]	BT	31	63.5	81	75	61.5 mo
Crook et al.[53]	BT	49	60	85.3	86.5	33.4 mo
De Crevoisier et al.[52]	BT	144	65	80	72	5.7 yrs

EBRT: external beam radiotherapy; BT: brachytherapy; FU: follow-up

Table 7: Penectomy versus conservative procedures in global series: local recurrence %

Author	Pts (n)	Penectomy (%)	Conservative procedures (%)
Mistry et al.[7]	65	12.5	28
Lont et al.[13]	257	4.5	35.3
Leijte et al.[8]	748	10	34
Ornellas et al.[6]	700	5.3	27.7

Predictive factors for local recurrence

In general, partial and total penectomy achieve better control than conservative procedures (Table 7) (LE 2a/b). In penile preserving procedures, when analyzing predictive factors for local recurrence, stage, grade and size[13,31,64] were not significant predictive factors, whereas positive margins seemed to be the best predictive factor for local recurrence in univariate ($p<0.0001$, $p=0.0353$)[13,25] and multivariate analysis (HR=2.9, $p<0.0001$)[13] (LE 2b), supporting the need for performing frozen biopsies during the surgical procedure in order to decrease positive surgical margins. However, there were no significant differences when comparing different penile preserving procedures (LE 3)[13].

Local recurrences in patients receiving preservation strategies have a tendency to develop at multiple sites. In a meticulous analysis of local recurrence, Meijer et al.[64] observed that 20% of this occurred outside of treated areas, probably related to the presence of undiagnosed pre-malignant lesions, and 48% in the treated area, showing insufficient therapy and therefore reinforcing the need to perform random biopsies of the glans epithelium before making the treatment decision, and to perform frozen section biopsies as part of the surgical procedure in order to avoid positive margins.

In patients treated with RT, tumor grade (p=0.402) and radiation dose (p=0.11)[54] were not significant predictive factors for local recurrence, but local stage (p=0.013) and size (<4 versus ≥4 cm) (p=0.05) were statistically significant factors in univariate and multivariate analysis (p=0.04).[52,69] In the series of Sarin et al. size was not significant (p=0.1) but tumor limited to the glans versus extension beyond the glans was a highly significant factor (p=0.0006) (LE 3).[54]

Impact of local recurrence on survival

Initial experience with conservative surgery had suggested that local control is significantly worse than with amputation (p<0.05). Lindegaard et al.[70] analysed 63 patients who were candidates for primary penile preserving surgery according to EAU criteria, 26 patients underwent partial or total amputation and 37 were treated with some form of penis conserving therapy. They found that local control rates were significantly lower for conservative therapy than amputation (5-year actuarial control rates of 69% and 100% respectively for T1 tumors), but overall survival was not affected, as most patients could be salvaged with radical surgery.[70]

In a series of 72 patients receiving penile preserving surgery, 3 (4%) developed local recurrence, 10 (13.8%) nodal metastasis and 2 (2.7%) died because of their tumor, but in this series no patient with local recurrence died because of his tumor.[4] In another series of 67 patients receiving laser treatment, 13 (19.4%) developed progression and 2 (3%) died of cancer, corresponding to 1 of 54 patients (1.8%) without local recurrence and 1 of 13 (7.6%) with local recurrence, with no statistically significant difference (p=.0346).[25]

In the series of Lont et al.[13] and Meijer et al.[64] when comparing patients with and without local recurrence, there was no significant difference in the development of nodal metastasis or cancer-specific survival (Table 8) (LE 2b). Surprisingly in the series of Lont et al. of patients with local recurrence, T1 tumors had high incidence of nodal metastasis, but with no significant difference compared to those without local recurrence Nodal metastasis in those with local recurrence developed in the same interval compared with patients who had no local recurrence, suggesting that the presence of other prognostic factors would account for this discrepancy.[13] In contrast, patients with local recurrence after partial penectomy had a significantly reduced cancer-specific survival compared to patients without local recurrence (p<0.0001) suggesting that local recurrence after partial penectomy reflects an aggressive behaviour of the primary tumor.[13]

Table 8: Impact of local recurrence on nodal metastasis development and survival

Local recurrence	Meijer et al.[64]		Lont et al.[13]	
	pN (1-3) (%)	CSM (%)	pN (1-3) (%)	CSM (%)
Yes	27.6	10.3	29.4	-
No	13.35	6.6	16.1	-
p	0.25	0.57	0.26	0.05 (T1) / 0.69 (T2)

CSM: cancer-specific mortality

Late recurrences

Although the vast majority of local recurrences occur during the first 2 to 3 years, late recurrences have been reported to occur after 6 to 28 years, showing the importance of long-term follow-up of these patients. Late recurrence was reported in 2.5% of the global series in 12% of local recurrences (LE 2b).[25,26,52,65,70,71] Consequently, long-term follow-up has been suggested in order to detect local recurrence. As there was no impact of local recurrence on survival,[13,64] a more relaxed follow-up schedule could be adopted. Nevertheless, the absence of data comparing the potential impact on survival between early and delayed detection also suggests that self-examination and close follow-up should be recommended (LE 3).[72]

PENILE RECONSTRUCTION AFTER PENECTOMY

Although the use of partial and total penectomy is decreasing in Western countries, penile reconstruction after these procedures is an increasing social demand. After partial penectomy the remaining penile stump is assessed for functionality and possible reconstruction. The length of the residual stump will dictate the methods for subsequent reconstruction.

Short penile stump

Depending on the location of the tumor and initial penile length the resulting stump may be short. Moreover, often the shaft length looks reasonable at the time of partial penectomy, but postoperatively the eventual outcome is disappointing, particularly on standing.

To avoid converting such patients to total penectomy and perineal urethrostomy, the suspensory ligament can be divided to help improve penile length by up to 2 to 3 cm (LE 3).[74] The mobilized penis is then resutured to the pubic bone. If the stump is tethered by the short shaft skin, the skin can be sutured to the proximal shaft and the distal denuded corpora covered with split-thickness skin graft. This technique creates a neo-glans appearance (similar to a glansectomy) that provides a cosmetic outcome better than conventional amputative surgery. An alternative method for skin coverage is the transfer of a superior scrotal graft (LE 3).[74,75] To improve the body image, voiding and sexual function, phalloplasty reconstruction can be performed in a delayed/staged fashion. Patients with a reasonable residual penile stump can be given extra penile lengthening, aside from suspensory ligament release, by dorsal V-Y plasty to lower the insertion of the scrotal skin.[3]

PENILE RECONSTRUCTION AFTER TOTAL PENECTOMY

Total penectomy with perineal urethrostomy, the so-called ‘toilet penectomy‘, is typically performed for stage T3 or T4 proximal penile cancers. In patients with no evidence of cancer recurrence, total phallic reconstruction can be considered in order to improve body image and psychosexual identity associated with total penectomy, especially in younger men (Figs. 12-13). Reports of total phallic reconstruction after penectomy for cancer are rare and typically employ a radial forearm free flap (LE 3).[76] The technical aspects of creating a neo-phallus after penectomy are very similar to that for a female to male gender reassignment operation[77] first described as a forearm free-flap based on the radial artery for phallic reconstruction (LOE 2b/3).

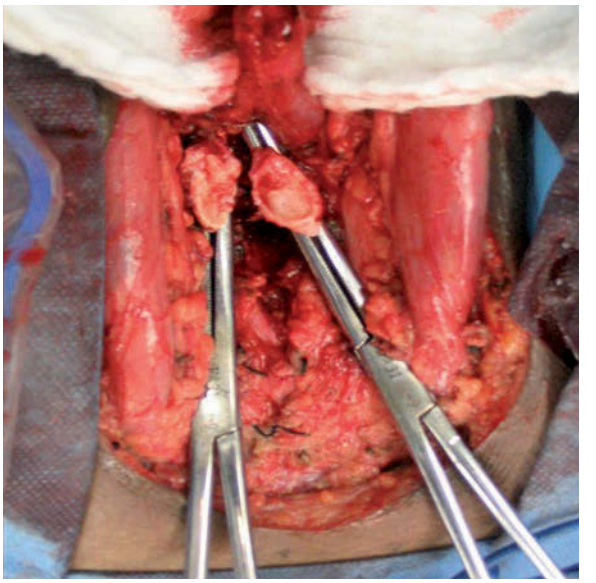

Fig. 12: *Total penectomy – crura of corpora cavernosa are clamped with artery forceps.*

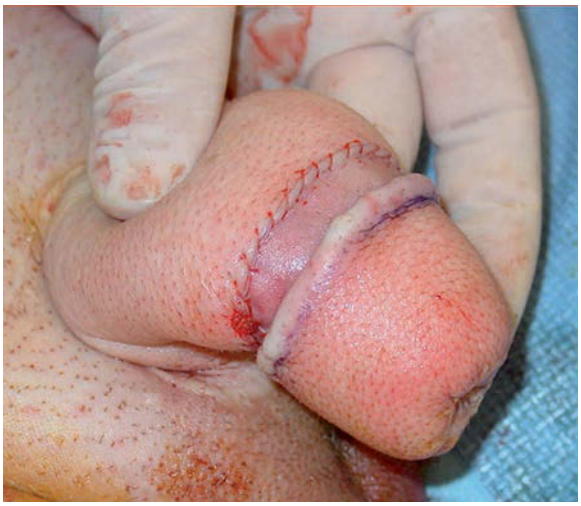

Fig. 13: *Penile reconstruction after total penectomy.*

Surgical technique: Two operative teams work simultaneously, one preparing the acceptor area and the other the flap. The free radial forearm flap is harvested from the forearm and shaped to a phallus, using a tube-in-a-tube technique while being attached to the forearm by its vascular pedicle. The corona and its sulcus are created using a skin flap and a skin graft. The neo-urethra involves de-epithelialising a strip of skin 0.5 cm wide 2.5 cm from the ulnar border of the flap. The free edge of the flap is sutured to the de-epithelialised strip over a 16-gauge Silastic catheter. The rest of the flap is wrapped around the neo-urethra and this free edge is also sutured to the de-epithelialised strip.

A second team simultaneously prepares the pubic area and inserts a suprapubic catheter into the bladder. The flap's pedicle is then divided and the urethral anastomosis is performed. The radial artery is microsurgically anastomosed to the common femoral artery, the venous anastomosis is performed under microscopic magnification to the saphenous vein. One forearm nerve (N. cutaneus antebrachi) is connected to the ilioinguinal nerve for protective sensation and the other nerve is anastomosed to the dorsal penile nerve for erogenous sensation. The defect of the donor area is covered with split-thickness skin graft harvested from the medial and anterior thigh. An inflatable penile prosthesis can be fitted subsequently for sexual function.

Technical modifications: Modifications to the original Chang and Hwang technique[77] are in differing designs of the skin island (such as cricket bat shape) and the relative position of the neo-urethral paddle in relation to the shaft coverage skin. The Biemer[78] modification centers the urethra portion of the flap over the artery (LE 2b/3).[21] Modifications of the Biemer[78] design also include the glans reconstruction method[79] (LE 2b/3), which when combined often offer the best cosmetic phalloplasty results (LE 4).[80]

The ideal candidate for such surgery is staged after a subtotal penectomy, where the corporal body ends are preserved, adequate urethral length is maintained with the creation of an infrapubic urethrostomy (instead of the traditional perineal urethrostomy). In highly selected young patients, penectomy can be successfully combined with immediate penile reconstruction (LE 3).[76] In a delayed fashion, an inflatable penile prosthesis can be successfully placed for sexual function (with an acceptable complication rate) (LE 3).[81] Myocutaneous abdominal flaps (Pryor technique),[82] latissimus dorsi free flap plus urethroplasty and prosthesis[83] and other myocutaneus flaps have been used for phalloplasty reconstruction.

Complications

The major advantages of this flap are that it is reliable, sensate, has a predictable anatomy, good sized vessels and pliable skin (LE 2b).[77,80] Major disadvantages are the donor site scar and deformity of the non-dominant arm, complexity of the surgery and the high complication rates, especially related to urethroplasty (37%-75%), complex urethral strictures (37%-64%), fistula (55%), and other complications related to the prosthesis (29%) or to the flaps (25%).[82-84] Nevertheless, global satisfaction with the neo-phallus evaluated by questionnaires was high (68%-93%).[82,84]

QUALITY OF LIFE

In patients with partial or total penectomy, when the remaining shaft of the penis is equal to or more than 4 cm it may still become erect and patients and their partners can reach orgasm and achieve normal ejaculation (LE 2b/3).[85] Recent

information about the significance of surgical margins[3,5] allows us to perform new surgical procedures, improving the anatomical integrity of the penis, although the incidence of recurrence is higher than with traditional methods. Nonetheless, the 5-year survival rate is similar, regardless of the therapy applied,[14] consequently the impact of each procedure on quality of life and the patients' preference is crucial in the treatment decision making process.

For this purpose we have selected 14 articles which include semi-structured interviews and self-administered international validated questionnaires (PAIS, GHQ, EORTC QLQ C-30, HAD, SPQ, APGAR or more specific IIEF, Lisat-11 checklist) for general state of health (5 articles), for sexual activity (9 articles, 3 of them also including cosmetic appearance). Another 7 articles with only patient and physician evaluation for both sexual activity and cosmetic appearance were also included for this analysis. In general, 7 items for sexual activity were included and each item was assessed in scales from 0 to 4 for increasing activity.

General state of health in urological malignancies

In patients with non-metastatic urological malignancies, studies on quality of life observed and recorded, in general, a significant deterioration of general state of health[86] (LE 2b) and a psychological impact with disturbances of body image, anxiety, self-esteem and sexual functioning (LE 2b).[87,88] All these findings are most obvious in the case of men facing penectomy or orchiectomy (LE 2b).[89]

General state of health in penile carcinoma

As a whole, all patients with penile carcinoma had moderately reduced sexual function, slightly reduced subjective well-being and social activity, working activity of approximately 25 hours a week during the first year. Around 25% of patients showed intrusive thoughts and avoidance, and mental illness was observed in 20% (LE 2b).[90] Another study including a control group confirmed previous data (LE 2b).[91]

Sexual function in penile carcinoma

We separated 4 treatment groups for analysis: 1) total penectomy and emasculation; 2) partial penectomy; 3) RT including external beam RT and brachytherapy; and 4) conservative surgical procedures, including laser treatment, Mohs procedure and penile preserving surgery.

Sexual interest: Patients who were treated with RT showed a high level of sexual interest (83.3%-100%) as was the case in those receiving conservative therapies (40%-80%) while only 17%-20% reported severely impaired or no sexual activity (LE 2b).[91-93] However, this item remarkably decreased in patients treated with partial penectomy, with percentages of 44.4%-64%, while 14%-45% of patients reported severe impact or no sexual interest (LE 2b).[91,92,94,95] In patients undergoing total penectomy or emasculation sexual interest was absent or severely impaired (LE 3).[91,92]

Enjoyment and satisfaction: With RT patients achieved a high level of satisfaction (83.3%-100%) with minimal severe negative impact (16.6%) (LE 3).[91,92] More controversial is the impact of conservative therapies, in one series analyzing only 5 patients, the satisfaction rate was 40% (LE 3).[91] However, in a more recent publication on patients receiving laser treatment, 72% stated that their sexual satisfaction was as good as before treatment (LE 2b).[93] Other authors using surgical conservative procedures corroborated these data (LE 3),[22] and with even better results in publications not using questionnaires (LE 4).[13,16,23]

In patients with partial penectomy the degree of satisfaction was lower than previous methods and varied from Europe, with a very low degree of satisfaction (18%-33.3%) to Brazil, with a satisfaction varying from 61.1% to 85.7% and with a low percentage (16.6%) being severely impaired (LE 2b).[94,95] This remarkable difference may be due to different cultural or education levels and life perspective. Total penectomy provided the lowest degree of satisfaction, close to 0% (LE 3).[91,92]

Coitus frequency: There is only one series analysing this item in patients receiving RT, maintaining frequency in 75%, with no attempts at intercourse in 16.6% (LE 3).[92] In patients treated with partial penectomy the frequency was substantially reduced, but with remarkable difference between Europe and Brazil. In Europe the frequency was reduced in 66.6%-82% of patients[91,92] (LE 2b) and it disappeared in 9%-44.4%. In contrast, in Brazil, the frequency was maintained in 33.3%-42.8%, slightly reduced in 35.7%-38.8% and disappeared in 21.4%-27.7% (LE 2b).[94,95] This difference can be explained by the same reasons reported for satisfaction. In the case of conservative therapies the frequency is highly maintained, 63% of patients treated with laser had sexual intercourse during the three months before the interview (LE 2b).[93] In total glans resurfacing, 85.7% of patients had sexual intercourse within 3 month after surgery (LE 3).[22] Other studies not evaluated by questionnaires corroborated these encouraging data (LE 4).[16,23]

Erectile dysfunction: In general, erectile function was highly preserved, regardless of the treatment method. Among patients who were previously potent, from 75%-83.3% resumed their potency after RT, although two series did not use questionnaires (LE 3).[53,54,91] A small difference was observed, 44.4%-66.6% of patients resumed their potency with penetration capacity when partial penectomy was performed (LE 2b).[91,94,95] In patients treated with conservative methods, 60% to 78% regained their potency within 3 months after laser treatment, and in only 10% of patients the dysfunction was due to the laser technique (LE 2b).[93] After using surgical techniques including partial or total glansectomy and resurfacing or grafting, Mohs technique, etc, almost 100% regained potency very quickly after healing, although glans sensitivity was reduced (LE 4).[16,22,23,31]

Partner relationship: On the whole there is no significant impact on this item, regardless of the treatment methods used, including the most radical (LE 2b). [92-94]

Identity: All groups of patients experienced little impact on sexual identity, regardless of the therapy applied, even with total penectomy ranging from 50%-100% (LE 2b).[91,92,94]

Other items related to sexual function: Libido was related to the treatment method (LE 2b).[91] Ejaculation was slightly affected by laser treatment (LE 2b).[93] Fellatio was less common, both before (22%) and after treatment (11%) (LE 2a).[96] There was a significant correlation between younger age and resuming or adding genital manual stimulation to the sexual repertoire, whereas no such statistical significance emerged among the few who were engaged in fellatio (LE 2a).[96] Masturbation was included in the sexual repertoire in 43% before treatment and almost all (95.6%) stated that the laser treatment had not affected their opinion regarding masturbation as a means of obtaining sexual satisfaction (LE 2a).[96]

Cosmetics: In one study 78% of patients who received laser treatment considered the cosmetic results satisfactory according to the questionnaire (LE 2b).[93] Two other studies dealing with penile preserving surgery reported satisfaction with cosmetic results in up to 100% with a reduced sample (LE 3).[15,22] With physician and patient evaluation of both laser and penis preserving surgery, satisfaction with the cosmetic results was also achieved in 100% of cases (LE 4).[13,16,23,31,37] Total glans resurfacing provided satisfactory cosmetic results in all patients (LE 2b)[16,17,22] although 14% mentioned that the skin of the penis felt slightly tight with erections (LE 2b).[22] After subtotal glans excision with or without grafting and after Mohs procedure, short-term cosmetic results were encouraging and voiding remained unchanged, with no reports of spraying, according to physician evaluation (LE 4).[15,31]

Evaluation by treatment methods

Partial penectomy: In patients with partial penectomy, the most altered domain is sexual function, in particular reduced sexual satisfaction and coitus frequency. This was affected to different degrees in European and Brazilian people, reflecting differences in cultural background and demography. These items are severely affected with total penectomy. In contrast, identity, sexual desire, and partner relationship have been preserved.

Radiotherapy achieved high scores in quality of life and sexuality. However, important biases have been observed in this evaluation. Among the four series which analyzed the quality of life related to RT, in the two comparative studies patients treated with RT were around 20 years younger than patients treated with partial penectomy or conservative therapy and age had a significant negative impact on sexual function ($p<0.001$).[90-92] In the other series only 2 patients were treated with RT.[91] In two other series evaluating sexual activity only 16.6% and 55% of patients were evaluable.[53,54] Cosmetic results were not mentioned in any series. For these reasons it is impossible to reach strong conclusions about quality of life in patients treated with RT.

Conservative surgical procedures: These procedures have a high level of global satisfaction similar to the general population, except for anxiety,[96] but the results are more consistent for laser treatment and highly promising with surgical procedures, although questionnaires were rarely used. Cosmetic results were generally very acceptable, both in questionnaires and in patient and physician evaluation.

General comments

As a whole, treatment for local penile cancer has a negative impact on the general state of health and sexuality, but this impact varies in different treatment modalities. A moderate psychological impact was observed. Around 20% of patients had mental illness, most often anxiety disorder; possibly from preoccupation with disease recurrence. As expected, the more radical treatment had the most impact on the patients' sexual life, even though some of the difference was due to age.

Conservative procedures with preservation of the penis seem to give the best results as regards sexual function with the strongest evidence and comparable to the whole population (LE 2a),[96] followed by RT, but this evidence remains weak as any bias may be observed. Around 20% of patients claimed that they would prefer treatment with lower long-term survival to increase their chance of remaining sexually potent (LE 2b).[92] On the other hand, patients who did not resume sexual activity after treatment had significantly lower levels of sexual satisfaction than those who did (LE 2a).[96] These comments suggest that all patients with localized penile carcinoma should receive professional sexual counselling as part of the treatment regimen before and after treatment. Multi-disciplinary follow-up with a psychologist trained in sex therapy is necessary and should begin when treatment is being decided to help patients and their partners.

RECOMMENDATIONS

Ta-Tis

5% 5-fluorouracil cream, 5% imiquimod cream, glans resurfacing, laser treatment, cryotherapy, photodynamic therapy, as first or second line are alternative procedures for these patients (LE 3; GR C).

T1G1-3 (of the foreskin)

For patients with an invasive tumor confined to the prepuce, a penile preserving strategy is strongly recommended by performing circumcision (LE 2b; GR B). Histopathological assessment of the surgical margin is essential (LE 2b; GR B). Careful assessment of the glans is required to exclude dysplasia or *in situ* disease (LE 3; GR B).

T1G1-3 (of the glans)

For patients who can guarantee regular follow-up, a penis-preserving strategy is strongly recommended (LE 2b; GR B). The choice of treatment is influenced by the size and position of the tumor on the glans and the side-effects of treatment**.** Although local recurrence did not have any negative impact on survival, meticulous follow-up or self-examination is advisable so that local disease recurrences can be treated as soon as possible (LE 3; GR C). Histopathological assessment of surgical margins is essential (LE 2b; GR B).

T2 (of the glans)

A conservative strategy of total glansectomy with or without resurfacing of the corporal tips is recommended (LE 2b; GR B). An alternative in very carefully selected cases is partial glansectomy for tumors encompassing less than half of the glans

in patients who will comply with close follow-up (LE 2b; GR B). A 20 mm macroscopic clear margin is not required (LE 2b; GR B).

T2 (of the corpora) and T3

Reconstructive surgery with margins dictated by frozen section analysis is an option in carefully selected cases (LE 3; GR B).

For large tumors involving more than the distal corpora, partial or radical amputation is considered standard (LE 2b; GR B).

Chemotherapy induction courses within the context of a clinical trial, followed by conservative procedures in case of complete or partial response, can be considered an investigational recommendation (LE 3; GR C).

Radiotherapy

RT is an alternative to conservative surgery for T1-T2 tumors (of glans), less than 4 cm in diameter. External beam or interstitial RT can be used, depending on the center's experience (LE 3; GR B). RT can also be used for T2 (corpora cavernosa invasion) or T3 tumors in inoperable patients (LE 4; GR C).

Local recurrences

Penile preserving strategy can be used again for local recurrence in patients treated initially with this approach (LE 3, GR C). Partial or total penectomy is indicated in patients with corpora cavernosa invasion or after RT (LE 2b; GR B). Only selected patients with non-invasive local recurrence after RT may be treated with penile preserving strategy (LE 4; GR C).

Penile reconstruction after total penectomy is an option in motivated patients after psychological evaluation and being made aware of the high rate of complications (LE 4; GR C).

Psychological support should be provided before therapeutic decision making, and thereafter, if possible (LE 2b; GR B).

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Committee 6

Management of the Lymph Nodes in Penile Cancer

Chair

Chris Heyns (South Africa)

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Vijay Sangar (England)

Boris Schlenker (Germany)

Yuvaraja Thyavihally (India)

Hein van Poppel (Belgium)

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Management of the Lymph Nodes in Penile Cancer

C. F. Heyns

N. Fleshner, V. K. Sangar, B. Schlenker, Y. B. Thyavihally, H. van Poppel

Introduction

Squamous cell carcinoma (SCC) of the penis can be surgically cured despite the presence of inguinal lymph node metastases, therefore appropriate management of the lymph nodes is extremely important in determining treatment outcome. However, due to the relatively low incidence of penile SCC, the limited patient numbers in published reports and the virtual absence of prospective, randomized clinical trials, there are numerous controversies about the optimal management of the lymph nodes in this malignancy.

In SCC of the penis with no inguinal lymph node metastases, the reported 5-year survival rate varies from 46% to 100%, with an average around 75%. In patients with lymph node metastases that were removed surgically, the reported 5-year survival rate varies from 0 to 86%, with an average around 60%. This wide variation depends on the extent of node metastases. In men with minimal node metastases (1-2 nodes) the reported 5-year survival rate varies from 75% to 88%, compared to an average of around 25% (7% to 50%) in those with more than 2 involved nodes, and around 5% to 10% in those with extranodal extension of cancer, lymph nodes larger than 4 cm in diameter or pelvic node metastases (LE 3).[1,2]

Overall 5-year survival rates in men with SCC of the penis after inguinal lymph node dissection (ILND) are shown in Table 1.[3] The data show that in node-positive patients ILND may be curative in approximately 20% to 60% of cases. However, it is also clear that even in node-negative men ILND does not guarantee 5-year survival, with treatment failure varying from 5% to almost 30% (LE 3).[3]

Table 1: Survival of men with SCC of the penis after inguinal lymph node dissection[3]

Author	Year	5-year overall survival (%)	
		Node-negative	Node-positive
Beggs and Spratt[4]	1964	72.5%	19.3%
Johnson and Lo[5,6]	1984	74%	-
Srinivas et al.[7]	1987	85%	32%
Pow-Sang et al.[8]	1990	80%	62.5%
Ornellas et al.[9]	1991	87%	29%
Ravi[10]	1993	95%	53%
Lopes et al.[11]	1996	-	40.3%
Pandey et al.[3]	2006	95.7%	51.1%

Despite this evidence, there appears to be considerable reluctance to utilize ILND, probably due to concerns about the reported high complication rate of this procedure. In a recent report on 454 patients registered between 2000 and 2003 in the National Penile Cancer Register in Sweden, ILND was performed in only 101 of 206 (49%) of those considered at high risk for inguinal metastases according to the EAU guidelines (G2-3 pT1 primary tumor).[12]

Selecting patients for ILND according to risk groups may be useful, but it has limitations. Leijte et al. reported that in the low-risk group patients (G1T1) the incidence of node metastases was only 6%, but in the intermediate risk group (G2T1) it was 54% and in the high-risk groups (G3T1, G1-3T2-3) it was only 37%, which means that 46% to 63% of these patients do not have inguinal node metastases.[13] Other recent studies have shown that the current EAU risk stratification guidelines have a low accuracy for predicting lymph node involvement, with the result that up to 82% of patients may undergo unnecessary prophylactic lymphadenectomy (LE 2).[14,15]

Evaluation of the patient

▪ Imaging

Ultrasound (US) of the inguinal lymph nodes, when performed by an expert, can be used to identify neoplastic nodes, which are characterized by the disappearance of the normal architecture where the normally present hilar fatty tissue is replaced by neoplastic conglomerates.[16-18]

Computed tomography (CT) and magnetic resonance imaging (MRI) are unreliable in staging impalpable regional lymph nodes. Even lymphotropic nanoparticle enhanced MRI (LNMRI) and positron emission tomography (PET)/CT cannot reliably detect micro-metastases.[19] In women with primary SCC of the vulva (a condition which has some similarities to SCC of the penis) routine CT scanning has also not been found useful in assessing inguinal node metastases (LE 3).[20]

CT or MRI can provide useful information in advanced cases, identifying those patients with enlarged pelvic or retroperitoneal nodes. With the exception of some rare published cases, all patients with pelvic node involvement always first had inguinal node involvement.[21,22] It has been suggested that CT of the abdomen and pelvis as well as chest radiography or other imaging studies should only be performed as clinically indicated (LE 3).[2]

▪ Antibiotics

It has been argued that, if palpable inguinal nodes become impalpable after 3-6 weeks of antibiotic treatment, this indicates that the nodes were enlarged due to infection and do not contain cancer. However, if the histopathological parameters of the primary tumor indicate a high risk for inguinal metastases, even if the nodes are non-palpable, antibiotic treatment will not change the necessity for further evaluating the nodes. After a 3-6 week course of antibiotic therapy, the presence of palpable inguinal nodes has been reported to decrease from 61% to 44%. This indicates that in only a small proportion of patients with palpable nodes antibiotic therapy could potentially change the further management of the nodes (LE 3).[23]

It has been suggested that, instead of giving 6 weeks of antibiotic treatment, immediate fine needle aspiration cytology (FNAC) of palpable nodes should be performed, with or without US.[21,22] However, antibiotics can be useful to minimize the risk of inguinal wound infection or septic complications due to an infected primary tumor (LE 4).[24]

▪ Cytology

FNAC was initially performed under fluoroscopic guidance using lymphangiography, but it is currently more often performed under US or CT control. Earlier studies reported an accuracy of 100%.[25] However, a false-negative rate of 20% to 30% has been reported.[26]

Although the reported sensitivity of US-guided FNAC has varied from 34% to 100% (depending on whether the nodes were clinically impalpable or palpable), the specificity varies from 91% to 100% (LE 2).[27-30] If tumor is confirmed, then therapeutic ILND can be performed instead of dynamic sentinel node biopsy (DSNB).

In a study of 44 women with primary SCC of the vulva US-guided FNAC had a false-negative rate of 9%, with no false-positive cytology results.[31] It has been suggested that US-guided FNAC may have a useful clinical role in the management of the groin nodes in vulvar carcinoma (LE 3).[20]

Lymph nodes that are hypoechoic or heterogeneous on US are suspicious of harbouring metastases. It has been suggested that in men with SCC of the penis US-guided FNAC of suspicious nodes should be the first investigation in clinically node-negative patients at high risk for occult metastasis. FNAC should also be used in patients with clinically palpable nodes and, if negative, can be repeated after a short delay. If the FNAC is positive, lymph node dissection (LND) should be performed, and overlying skin and tissues containing the needle tract should be removed with the nodal tissue (LE 3) (Fig. 1).[21]

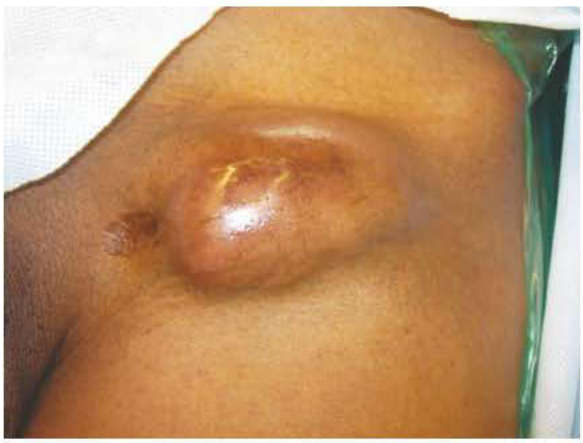

Fig. 1: *Visible inguinal node metastasis, in which the diagnosis can be confirmed with fine needle aspiration cytology prior to surgery.*

▪ Sentinel node biopsy (SNB)

It has been reported that in men with SCC of the penis random inguinal node biopsies performed superficially have an approximately 50% false-negative rate, whereas biopsies of palpable nodes have an approximately 10% false negative rate (LE 3).[32]

In a study of dynamic sentinel node biopsy (DSNB) performed in 129 patients with T2 or T3 penile SCC the false-negative rate was 15% when calculated per groin dissection, and 17% when calculated per patient.[33,34] There appears to be a "learning curve" for DSNB, because with experience over several years in a single centre the false-negative rate decreased from 19.2% to 4.8% (LE 3).[13] However, a false-negative rate as high as 43% has been reported for DSNB using an isolated gamma probe technique (LE 3).[35] In other studies the sensitivity of DSNB was 71% to 80%, with a false negative rate of 1% to 20% (LE 3) (Fig. 2).[36-38]

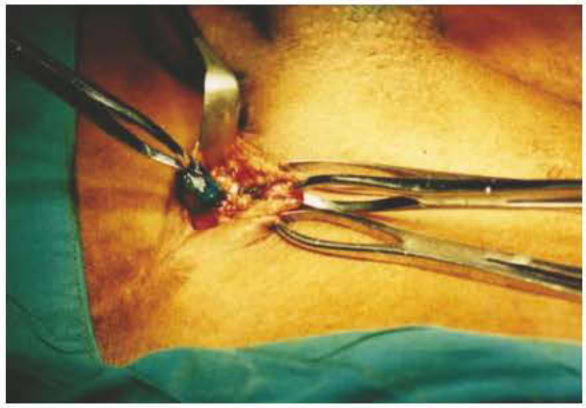

Fig. 2: *Dynamic sentinel node biopsy (note blue dye at base of penis and in exposed inguinal lymph node).*

A review of 7 series of patients without palpable inguinal adenopathy who underwent conventional SNB showed a recurrence rate of 16%. Extending the dissection to a wider region did not improve these results (20% recurrence). DSNB had a false negative rate of 18%. It has been suggested that superficial and modified inguinal dissection techniques with intraoperative frozen section remain the "gold standard" for defining the presence of microscopic metastases (LE 3).[39]

Catalona et al. suggested that SNB is not indicated in patients with clinically positive nodes.[40] Recent studies by Hungerhuber et al. and Heyns and Theron showed that in patients with clinically palpable nodes DSNB is of low value for detection of lymphatic spread, with a false negative rate of 13% (LE 3).[41,42]

▪ Predicting inguinal node metastases

There is a clear relationship between certain histopathological features of the primary tumor and the probability of lymph node metastases.[43-45] Ficarra et al. have developed a nomogram including several clinical and pathologic variables

to estimate the risk of lymph node involvement at follow-up. These factors include tumor thickness, microscopic growth pattern, Broders' grade, presence of vascular or lymphatic embolization, infiltration of the corpora cavernosa, corpus spongiosum or urethra, and the clinical stage of inguinal lymph nodes (LE 3) (Figs. 3, 4).[46,47]

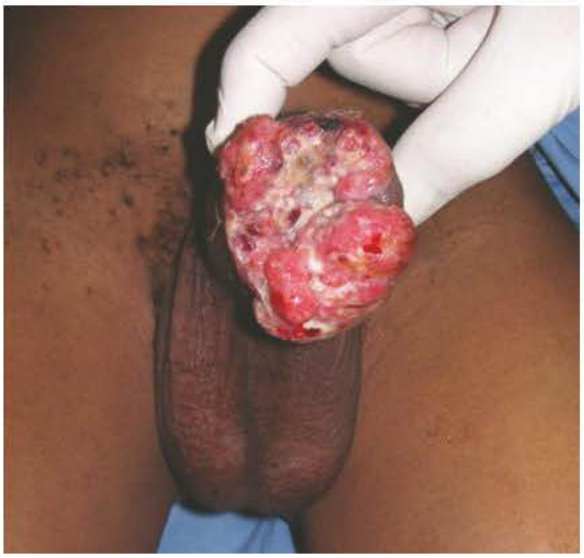

Fig. 3: *Grade 3 Stage T3 SCC of the penis, which has a high risk of inguinal node metastases.*

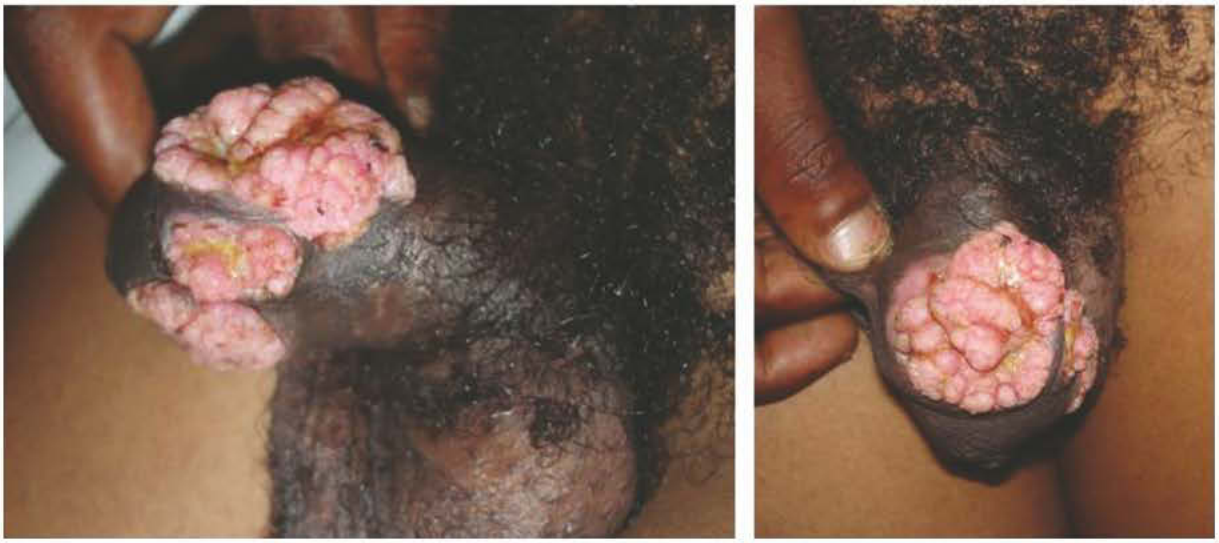

Fig. 4: *Verrucous carcinoma of the penis, which has a low risk of inguinal node metastases.*

Cubilla has pointed out that biopsy of the primary tumor is not useful for the evaluation of some of these prognostic factors, so a resected specimen should be utilized (LE 4).[48] This raises the question whether the nomogram is reliable in patients undergoing penile-conserving treatment such as radiotherapy, brachytherapy or laser ablation. Furthermore, external validation of the nomogram is still lacking.

It has also been suggested that the size or diameter of the primary tumor is related to the risk of tumor spread to the inguinal nodes, even though the currently recommended risk stratification groups and nomograms do not take tumor size into account (LE 3).[49,50] It has been suggested that tumor grading has a substantially stronger impact on the metastatic risk in T1-2 penile carcinoma, indicating the need for surgical lymph node staging starting at the G2pT1 stage (LE 3).[51,52]

A study of 158 patients who underwent DSNB showed that the size of the sentinel node metastasis was the only significant prognostic variable for additional lymph node involvement. None of the groins with only micrometastasis (2 mm or less) in the sentinel node contained additional involved nodes, suggesting that these patients can be spared contralateral LND (LE 3).[53]

Surveillance

After treatment of the primary tumor, surveillance of the inguinal areas has the advantage that surgery and its potential complications may be avoided, but the disadvantage is that delayed diagnosis and treatment of inguinal metastases may miss the opportunity of cure.

In an earlier report of patients followed with surveillance, inoperable node disease developed in 22%, partly because patients did not comply with the proposed follow-up schedule (LE 3).[54] In a study of 150 patients with carcinoma of the penis, those with nonpalpable nodes (n = 77) were kept under surveillance. Metachronous inguinal node metastases developed in 16 patients (21%) among whom surgical lymphadenectomy was possible in 12 (75%) while 4 had unresectable metastases (LE 3).[55] Obese patients have an increased risk of complications after lymphadenectomy, but the palpation of enlarged nodes during follow-up is also more difficult (LE 4).[56]

It has long been accepted that patients with small, well-differentiated primary tumors that do not invade the corpora and who have no palpable nodes can be followed carefully at 1-3-month intervals after treatment of the primary tumor, but that if compliance with this "expectant management" is doubtful, bilateral superficial ILND is preferable (LE 4).[57-60]

It is also generally accepted that suspect lymph nodes that are found during follow-up must be surgically removed (LE 4).[61] However, it has to be kept in mind that clinical evaluation of the lymph nodes is not highly reliable in determining the presence of malignancy, therefore US evaluation with FNAC is advisable before extensive surgery is undertaken.

It has been suggested that in patients with G1T1 tumors surveillance is the preferable approach. In G2-3 T1-2 patients other factors such as age, socio-economic status, cultural level and obesity (which influence the compliance with followup and the reliability of surveillance) should be taken into account when deciding on ILND versus surveillance (LE 3) (Fig. 5).[62]

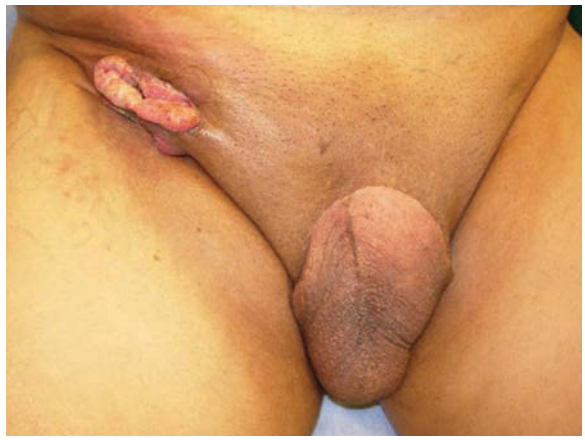

Fig. 5: *Ulcerating inguinal node metastases in a patient on surveillance after total penectomy, who did not return for regular follow-up.*

Ravi compared prophylactic lymphadenectomy (n = 113), observation (n = 258) and inguinal biopsy (n = 52) in a non-randomised fashion, and reported 5-year disease-free survivals of 100 and 76%, respectively, for node-positive patients in the lymphadenectomy and observation groups (LE 3).[63]

Horenblas et al. reported on 110 patients with SCC of the penis. Surveillance was used in 57 of 66 who presented with non-suspicious nodes and 5 of 40 with clinically suspected nodes. Overall, 25 patients had a regional recurrence (25/62 on surveillance = 40%), 5 of whom (5/25 = 20%) could be cured subsequently. The authors recommended surveillance of the regional lymph nodes in G1-2T1-2cN0 categories (LE 3).[43]

In a prospective nonrandomized study of 64 patients with carcinoma of the penis and clinically negative nodes, 19 were followed up with surveillance, and relapse occurred in 7/19 (37%) in the surveillance group (LE 3).[64]

A retrospective study of 36 patients followed up regularly by the same person showed that of the 27 patients who presented with negative groin lymph nodes, 10 (37%) had a delayed LND, 3 died within 1 year of surgery, 4 were alive at 3 years and 3 were lost to follow-up. In total, 17 patients (47%) did not require lymphadenectomy and 14 (82%) of these patients were alive at 3.8 years, the other 3 being lost to follow-up. The authors concluded that a careful, closely monitored

follow-up protocol can eliminate the need for lymphadenectomy in select patients with penile cancer (LE 3).[65]

A study of 42 patients with stages T1-3N0M0 SCC of the penis suggested that those with grade 1 tumors may be offered either careful surveillance or prophylactic bilateral ILND, depending on the clinical circumstances and patient preference (LE 3).[66]

A study of 82 patients showed that regional control and survival were not significantly improved by prophylactic lymphadenectomy. The results supported penis-conserving therapy and watchful waiting for early-stage disease.[67] Another study of 56 consecutive patients suggested that motivated low-risk patients (G1-2 pT1-2) could be included in a surveillance program (LE 3).[41]

A review of 51 patients with invasive penile cancer showed no significant difference related to regional recurrence between surveillance, inguinal radiation and lymphadenectomy for stage N0 tumors (LE 3).[68]

A study of 101 patients suggested that radiotherapy for the primary lesion carries a significant risk of loco-regional recurrence, which mandates close follow-up.[69] A report on 102 patients who underwent conservative treatment of the primary lesion (brachytherapy alone or with limited surgery) found that 9 of 28 (32%) patients with local relapse died of their neoplasms compared to 21 of 28 (75%) patients with lymph node relapse, showing that node relapses remain a major cause of death (LE 3).[70]

A study of 46 patients with penile carcinoma showed that those with pT1 tumors and depth of invasion 5 mm or less had little risk of inguinal node metastasis, suggesting that close observation of reliable patients meeting these criteria may be a safe alternative to prophylactic lymphadenectomy (LE 3).[71]

Lont et al. reported a non-randomized study in which 85 patients were treated with initial surveillance of the regional lymph nodes and 68 patients underwent DSNB. Disease-specific 3-year survival in the surveillance and sentinel node groups was 79% and 91%, respectively. There was a greater number of involved lymph nodes and more extranodal extension (95% versus 13%) in the surveillance group compared with the SNB group. The higher metastatic load in the surveillance group also induced more treatment related morbidity because of the perceived need for adjuvant treatment, which was usually external radiation therapy (LE 2).[72]

A recent review suggested that men at a higher risk for local or regional recurrence who should have more rigorous follow-up include:[73]

1. those treated with phallus-sparing strategies such as laser ablation, topical therapies, or radiotherapy;
2. patients with clinically negative inguinal lymph nodes who are managed without lymphadenectomy despite high-risk primary tumors (G3, pT2-3, vascular invasion);
3. those with lymph node metastases after lymphadenectomy.

Good candidates for less stringent surveillance include:

1. patients with low-risk primary tumors (G1-2, pTis, pTa (verrucous carcinoma), pT1 with no vascular invasion) and
2. those with negative inguinal nodes after lymphadenectomy whose primary tumors were managed with partial or total penectomy (LE 4).[73]

The following surveillance protocols have been recommended:

1. for low-risk patients: physical examination every 3 months for the first 2 years, every 4 months for the third and fourth years, and yearly thereafter; CT is used only in those who are obese or have a history of prior inguinal surgery;
2. for high-risk patients: physical examination every 2 months for the first 2 years, every 3 months for the third year, every 6 months for the fourth year, and yearly thereafter.

Laboratory studies and chest radiography are performed yearly for the first 3 years. CT is used only for patients who are obese or have had in-

guinal surgery, to be performed every 4 months for the first 2 years and every 6 months for 1 year thereafter (LE 3).[73]

In a prospective study of 50 patients Pompeo concluded that ideal candidates for watchful waiting after primary lesion treatment are those who do not have primary lesions greater than 2 cm in diameter, unfavorable histology findings, invasive lesions, or palpable nodes (LE 3).[49]

Timing of inguinal lymph node dissection (ILND)

In 1907 Young recommended simultaneous penectomy and bilateral ilio-inguinal lymphadenectomy for carcinoma of the penis. However, early surgical reports enumerated many complications, resulting in the development of negative attitudes toward ilio-inguinal lymphadenectomy (LE 3).[74] The procedure was modified in the 1930s, where the primary tumor was removed and the node dissection was performed later to allow time for presumed infection to resolve, and for metastatic cells to embolize from the primary tumor to the lymph nodes (LE 3).[22]

With regard to timing, ILND can be defined as:

1. early or prophylactic when performed within 6 weeks after treatment of the primary lesion in patients without palpable nodes;
2. delayed or therapeutic when performed for the development of palpable inguinal nodes during follow-up.[32]

Earlier studies suggested that patients with tender, enlarged inguinal lymph nodes should be observed for up to 3 months following primary treatment, as a large percentage of these nodes are inflammatory and subside spontaneously.[75] Later studies recommended waiting for 6 weeks after eradication of the primary lesion before lymphadenectomy (LE 4).[8,76]

Two major reasons for delaying ILND have been proposed:

1. to provide time for metastatic cells to embolize from the primary tumor to the lymph nodes, thus avoiding the potential risk of metastases in the tract between the primary tumor and the nodes;
2. to give antibiotic treatment, so that enlarged inflammatory nodes can regress, thus possibly avoiding unnecessary LND, and decreasing the risk of infection if ILND is performed (LE 4).[22,56]

Some earlier studies reported virtually no deaths and good results by delaying lymphadenectomy until there was proof of node metastases.[4,32,77-79] However, other authors recommended immediate ILND in patients with large and moderately to poorly differentiated primary tumors, and in patients with persistently palpable nodes after eradication of the primary lesion and 6-8 weeks of antibiotic therapy (LE 4).[57,59,80]

Johnson and Lo reported 3- and 5-year survival rates of 71% and 57% in patients who underwent early therapeutic ILND, compared with 50% and 13%, respectively, in patients who underwent late therapeutic dissections, suggesting that a "wait and watch" policy in patients with clinically negative nodes at diagnosis is not justified (LE 3).[6] McDougal reported a 5-year disease-free survival for Jackson stages II and III (palpable inguinal nodes) of 88% and 66%, respectively, when lymphadenectomy was performed shortly following treatment of the primary lesion, compared to only 38% and 0, respectively, if the primary lesion was treated locally and no lymphadenectomy was performed (LE 3).[81] Fraley et al. reported a 5-year survival of more than 75% in patients who underwent penectomy and immediate ILND, compared with 6% in those who underwent delayed ILND when inguinal metastases developed (LE 3).[82] Ravi reported 5-year disease-free overall survivals of 94%, 93% and 85%, respectively, in patients with invasive penile cancer and negative inguinal nodes subjected to prophylactic lymphadenectomy, observation or inguinal biopsies in a non-randomised fashion. The 5-year disease-free survivals of node-positive patients in the lymphadenectomy and observation groups were 100 and 76%, respectively (LE 3).[63]

A review published in 1993 concluded that awaiting the development of node metastasis carries the risk of a significantly lower survival time. It

was recommended that all patients with clinical T2-T4N0 SCC of the penis should undergo immediate ILND (LE 4).[83] A study of 414 patients reported a better 5-year survival rate for patients who underwent lymphadenectomy concomitantly with penile surgery compared to those who underwent delayed lymphadenectomy (LE 3).[84] A study of 78 patients who had undergone 135 groin dissections concluded that in developing countries where patients do not come for regular follow-up and often present with fungating inguinal secondaries, a policy of early bilateral regional node clearance despite the level of morbidity is preferable (LE 3).[85] A smaller study of 23 cases concluded that early versus delayed lymphadenectomy carries an acceptable morbidity and can benefit patients with positive nodes (LE 3).[23]

McDougal concluded from a study of 76 cases that removing groin nodes which are microscopically positive improves the survival rate over that of delayed lymphadenectomy (LE 3).[86] A report on 42 patients recommended prophylactic bilateral ILND in patients with primary tumors other than grade 1, since surveillance will not spare these patients eventual lymphadenectomy and may potentially compromise survival by delaying surgery (LE 3).[66]

Reviews of the literature show 5-year survivals ranging from 57% to 88% for immediate and 8% to 38% for delayed lymphadenectomy (LE 3).[1,87] Several authors have concluded that early ILND is likely to improve the outcome in patients with infiltrating penile SCC (LE 4).[87-93]

In a retrospective study of 40 patients who initially presented with bilateral impalpable lymph nodes, Kroon et al. found that on multivariate analysis early resection of occult inguinal metastases detected on DSNB was an independent prognostic factor for disease specific survival, showing that early resection of lymph node metastases in patients with penile carcinoma improves survival (LE 3).[33]

Mortality has been reported only in cases in which lymphadenectomy was done concomitantly to penectomy and in the presence of sepsis (LE 3).[87] A recent review concluded that ILND is best performed after a course of antibiotic therapy if the primary tumor is infected, although the duration of antibiotic therapy prior to lymphadenectomy has not been formally studied (LE 4).[94]

In most recent studies ILND was performed 4-6 weeks after penectomy.[88,95,96] A more recent review stated that, typically, there is a 2-week interval between surgery for the primary penile lesion and the node dissection for the following reasons: (1) to allow the patient to recover from the penile surgery (2) to obtain pelvic MRI and (3) to evaluate the histopathology of the primary lesion, which indicates the risk of node metastases (LE 4).[97]

In a recent study of lymphadenectomy in 19 patients, only 4 underwent penectomy and standard lymphadenectomy simultaneously.[98] In another recent study 26 patients underwent penectomy and bilateral modified ILND at the same operative time, with no increase in the complication rate.[99]

Theron and Heyns reported on penectomy and simultaneous bilateral radical ILND performed in 18 patients with T2-3 primary lesions and palpable inguinal nodes.[100] The complications were compared with a previous study of 34 men who underwent bilateral ILND at a mean of 72 days after penectomy at the same institution. Postoperative complications occurred in 61% of the patients in the simultaneous and in 76% in the non-simultaneous ILND group. The authors concluded that penectomy with simultaneous bilateral ILND does not lead to a higher complication rate compared with ILND deferred for 10 weeks after penectomy (LE 3) (Fig. 6).[100]

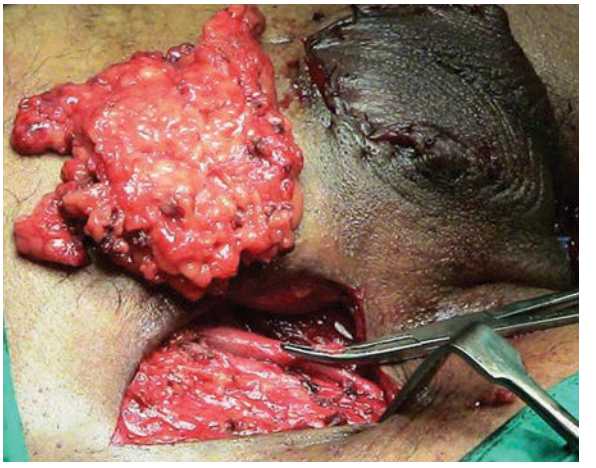

Fig. 6: *Complete ILND performed at the same time as total penectomy (note artery forceps on transected large saphenous vein).*

Thyavihally et al. reported on 114 patients who underwent ILND and penectomy at the same time.[101] Bilateral superficial ILND was done in 18%, bilateral ilio-inguinal dissection in 63% and unilateral ilio-inguinal and contralateral superficial LND in 19% of patients. Minor flap necrosis was seen in 18%, major flap necrosis in 5%, minor wound infections in 3%, temporary unilateral lymph oedema in 2% and seroma formation in 4%. The authors concluded that ILND can be done safely along with primary surgery without increased wound related morbidity, which is particularly important in situations where follow-up is unreliable (LE 3).[101]

Anatomical considerations

There are several subtle but potentially confusing differences in the anatomical terms used by different authors. These differences involve the description of the fascial layers, the grouping of lymph nodes as well as the drainage channels from penile structures.

Crawford gave the following descriptions: the superficial fascia of the lower abdomen is composed of Camper's and Scarpa's fasciae. Camper's fascia, the most superficial, continues uninterrupted onto the thigh, whereas Scarpa's fascia fuses with the fascia lata approximately 1 cm below the inguinal ligament, forming Holden's line (groin crease).[74,102]

The fascial layers of the thigh are described as:

1. superficial fascia, composed of two layers:
   a) a fatty or superficial layer of the superficial fascia
   b) a membranous layer of the superficial fascia of the thigh (Camper's fascia).
2. deep fascia (fascia lata) deep to Camper's fascia. This fascia is thinnest on the medial side of the thigh and thickest on the lateral aspects. The saphenous opening is formed by the fascia lata, and the greater saphenous vein pierces not only the deep fascia (fascia lata and cribriform fascia) but also the femoral sheath to enter the femoral vein.[74,102]

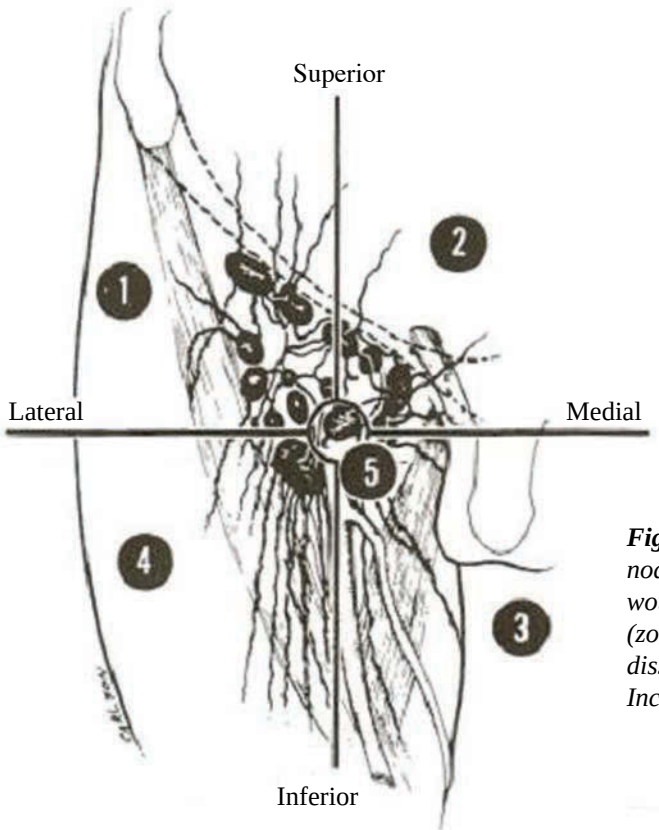

Fig. 7: *Zonal anatomy of the superficial inguinal nodes as described by Daseler (the sentinel node would be expected to be in the superomedial zone (zone 2) (from Johnson DE, Arnes FC – Groin dissection. Chicago, Year Book Medical Publishers, Inc, 1985, pp.15-16).*

Other authors gave a somewhat different description of the inguinal nodes [103-108]. Historically, the following terms were used to describe the nodes:

1. superficial inguinal nodes: those parallel to the inguinal ligament
2. superficial femoral nodes: the vertical chain adjacent to the long saphenous vein
3. deep femoral nodes: those in direct relation to the femoral vessels.

The current anatomical convention is that all nodes distal to the inguinal ligament are called inguinal, and are divided as follows:

1. Superficial inguinal nodes: located deep to Scarpa's fascia but superficial to the fascia lata (8-25 nodes). They can be divided by a line drawn horizontally through the junction of the greater saphenous vein and the femoral vein into:
   a) superior (or high or inguinal) superficial nodes – parallel to the inguinal ligament, with medial and lateral groups
   b) inferior (or low or femoral or subinguinal) superficial nodes;
2. Deep inguinal nodes: deep to the fascia lata and medial to the femoral vein (3-5 nodes); the most consistent of the deep inguinal nodes and frequently the only one present is the lymph node of Cloquet or Rosenmüller, situated in the femoral canal between the femoral vein and the lacunar ligament.[103,108]

Alternatively, the deep inguinal nodes are described as those situated around the fossa ovalis, where the saphenous vein drains into the femoral vein.[109] So, there seems to be some confusion about the terms deep inguinal and femoral nodes.

Micheletti et al. suggested that the term inguinofemoral should be used when referring to the nodes in the femoral or Scarpa's triangle.[106] They can be divided into two compartments, superficial or deep to the femoral fascia:

1. superficial, with two categories:
   a) superficial inguinal nodes lying along the inguinal ligament
   b) superficial femoral nodes lying vertically along the great saphenous vein before it enters the femoral vein, at the fossa ovalis
2. deep femoral nodes - situated within the fossa ovalis covered by the lamina cribrosa, medial to the femoral vein (LE 3).[104-106]

Lymph from the penile skin drains to the superficial nodes, especially the superomedial zone, and there is cross-over to both sides - the superficial lymphatics decussate at the base of the penis, accounting for occasional bilateral involvement (LE 3).[32,110] It is accepted that the deep inguinal nodes drain lymph from the superficial nodes or directly from the deeper structures of the penis. However, it has been stated that from a clinical perspective the anatomical distinction between superficial and deep inguinal nodes is useless, as they can not be distinguished from each other on physical examination (LE 4).[109]

The pelvic (iliac) nodes are located around the iliac vessels and in the obturator fossa (12-20 nodes). There is some controversy as to:

1. whether lymph from the penis can drain directly into the iliac lymph nodes without first draining into the inguinal nodes;
2. whether there is a prepubic node;
3. whether any lymph nodes are situated deep to the deep fascia;
4. whether there are any deep nodes distal to the sapheno-femoral junction.

Some authors stated that lymph from the glans and corporal bodies may drain not only into the superficial inguinal, deep inguinal or femoral nodes, but may drain directly to the external iliac nodes.[32,110] However, Riveros et al. and Cabanas did not find any lymphatic channel that drains into the iliac lymph nodes without first draining into the inguinal nodes (LE 3).[111,112] Furthermore, clinical studies have shown that involvement of the pelvic lymph nodes without involvement of the inguinal lymph nodes is exceedingly rare.

According to Spratt[108] the prepubic node is occasionally found in the subcutaneous tissue anterior to the pubic symphysis, forms part of the superficial inguinal nodes, and receives channels

from the penis. He suggested that when operating for penile cancer the areolar tissue overlying the pubis must be removed cleanly to ensure resection of the presymphyseal lymphatics and nodes (LE 4).[108] However, there appears to be little evidence to support this concept, anatomically or clinically.

Some authors state that the deep layer of the subinguinal nodes is located under the fascia lata within the femoral sheath. There are generally 3 nodes in this set. One is located inferior to the saphenofemoral junction, the second in the femoral canal, and the third at the femoral ring (node of Cloquet or Rosenmüller).[102] It seems clear that the number of such nodes is very variable, seldom more than 3, and may be nil. Some authors regard the most proximal (Cloquet's or Rosenmüller's node) as the most constant, but others regard it as the least constant. According to Hudson et al., the cribriform fascia has a very indistinct distal border, as compared with the crescentic upper margin, therefore some of the proximal nodes of the vertical superficial inguinal chain might appear to be deep 'femoral' nodes (LE 3).[103] A study of 50 female cadavers demonstrated that the deep femoral nodes are always situated within the fossa ovalis, and that no lymph nodes are located lateral to the femoral artery beneath the fascia lata (LE 3).[113]

Earlier descriptions stated that the deep inguinal nodes surrounding the femoral vessels within the femoral sheath may extend distally into the adductor canal.[74] An anatomical study of 50 cadavers by Borgno et al. found that no lymph nodes are located beneath the femoral fascia distal to the inferior margin of the fossa ovalis, i.e. distal to the sapheno-femoral junction (LE 3).[113] A study of 20 cadavers by Hudson et al.[103] found no nodes deep to the deep fascia distal to saphenous opening. However, in the cribriform fascia covering the saphenous opening, some nodes of the superficial group may occur within fenestrations of this fascia, which may account for the historic descriptions of deep femoral nodes distal to the sapheno-femoral junction.[108] It has been suggested that just distal to the femoral sheath there is no clear demarcation between superficial and deep inguinal lymph nodes (LE 3).[103]

Spratt suggested that neither the removal of deep fascia in the femoral triangle nor its incision, with consequent stripping of the femoral vessels in the thigh, is normally necessary in a radical groin node dissection.[108] Hudson et al. stated that there is no good evidence to support wide excision of the deep fascia of the femoral triangle with distal stripping of the femoral vessels in the operation of 'complete' ILND. It is possible to clear inguinal nodes, both superficial and deep, without excising the deep fascia. However, they stated that where the intention is to remove only superficial inguinal lymph nodes, the fossa ovalis should be cleared and the sapheno-femoral junction cleaned (LE 3).[103] The rationale for superficial dissection is that two series have shown no positive nodes deep to the fascia lata unless superficial nodes were also positive (LE 3).[114,115]

On the basis of lymphangiographic studies Cabanas described a sentinel lymph node located close to the superficial epigastric vein.[61] Anatomical studies showed that the sentinel lymph node area has up to 7 lymph nodes located between the superficial epigastric vein and the external pudendal vein. However, even by extending the area of dissection and removing all lymphatic tissue in the area of the superficial epigastric vein, and all the nodes medial to the saphenous vein, the true sentinel node can be missed (LE 3).[109]

Sentinel node biopsy (SNB)

Sentinel node biopsy (SNB) in patients with SCC of the penis and clinically negative inguinal regions was proposed by Riveros et al. and Cabanas, based on anatomic dissections and studies of lymphangiograms. A 5-cm incision is made parallel to the inguinal crease and centered two fingerbreadths lateral and two fingerbreadths inferior to the pubic tubercle. By insertion of the finger under the upper flap toward the pubic tubercle, the sentinel lymph node is encountered and excised (LE 3).[111,112]

However, subsequent studies reported a significant false negative rate (up to 25%) for SNB (LE 3).[116-118] Possible reasons for false negative SNB appear to be:

1. misidentification, because the location of

the presumed sentinel node is based on anatomical position and not on physiological demonstration of lymphatic drainage in the individual patient;

2. inadequate sectioning and histopathological examination of the node, thus overlooking microfoci of metastasis;
3. a long time lapse between SNB and groin dissection, resulting in lymphatic permeation and metastases along alternative channels.[119]

Pettaway et al. evaluated an "extended" SNB, during which all of the lymph nodes between the inguinal ligament and the superficial external pudendal vein were removed. However, this approach was later abandoned because it resulted in a false-negative rate of 15% to 25% (LE 3).[120]

Modified (limited) ILND

Fraley appears to have been the first to propose, prior to 1984, that the standard ILND could be modified by not ligating the saphenous vein in order to reduce the incidence of postoperative complications.[57] However, Johnson and Lo warned that a less than complete lymphadenectomy could increase the risk of tumor recurrence (LE 4).[5]

A modification of the standard complete ILND was reported in 6 patients by Catalona in 1988.[121] It was designed to provide staging information and therapeutic benefit similar to standard extended lymphadenectomy with less morbidity. The modifications included:

1. shorter skin incision
2. preservation of the subcutaneous tissue superficial to Scarpa's fascia
3. no dissection lateral to the femoral artery or caudal to the fossa ovalis
4. preservation of the saphenous vein, and
5. elimination of sartorius muscle transposition.

All of the superficial lymph nodes within the described area are removed, as are the deep inguinal nodes medial to the femoral vein up to the inguinal ligament.[121] Therefore, the perception that this is a purely "superficical" node dissection is not supported by the original description of the technique. The procedure has become known as a "modified" ILND, but "limited" ILND is perhaps a more accurate term.

In a recent study of 50 patients who underwent DSNB the groin was divided according to Daseler's five zones. All the sentinel nodes were located in the superior and central inguinal zones. No lymphatic drainage was seen to the inferior two regions of the groin. This suggests that the extent of inguinal node dissection could be limited to removal of the superior and central inguinal zones (LE 3).[122] However, it is assumed that this includes superficial as well as deep nodes in the relevant areas.

In a long-term follow-up study of 12 consecutive men who had undergone modified ILND, no major or permanent complications occurred and no patient had recurrent disease.[123] However, other studies have indicated that the false-negative rate for this procedure ranges from 0% to 15% (LE 3).[99,124]

Ravi et al. proposed an "inguinal pick" procedure as an alternative to previously described selective biopsies. It included an elaborate biopsy of all identifiable nodes in the inguinal region, including the sentinel node area. They reported an overall 72% sensitivity in detecting regional spread and 5-year survival rates of 100% and 83% in inguinal pick node positive and node negative patients, respectively (LE 3).[125] However, 7 of 47 (15%) patients with negative initial node picking developed metastases later and the 5-year survival in this group was significantly lower than for the initially positive cases.[125]

A review of 94 women with clinical T1N0M0 SCC of the vulva concluded that a superficial ILND resulted in an excess of groin recurrences (3/76 = 4%) compared to a full femoro-inguinal groin node dissection (LE 3).[126] In two studies of women with SCC of the vulva, modified lymphadenectomy with preservation of the saphenous vein did not result in a lower complication rate (LE 3).[127,128]

In a study of 10 women with SCC of the vulva, radical lymphadenectomy with excision of the

fascia lata and exposure of the femoral vessels and nerve was performed on one side, while a more conservative procedure (directed at removing the nodes as described in anatomical textbooks) was performed on the other side. Lymph node retrieval was equal, but the subjective short-term morbidity was reduced with the more conservative surgery (LE 3).[129]

In women with invasive SCC of the vulva, Micheletti et al. proposed doing a deep femoral lymphadenectomy (removing lymphatic tissue from the anterior and medial surfaces of the femoral vein within the fossa ovalis) with preservation of the fascia lata and cribriform fascia. In a study of 42 patients the number of superficial and deep femoral lymph nodes removed (mean 20, range 8-32) was similar to the number reported in anatomy books, and the 5-year survival rate was comparable to that in the literature (LE 3).[104] In a further study of 156 women with SCC of the vulva the saphenous vein was ligated at distal and proximal ends and removed *en bloc* with the superficial inguinal nodes as well as the deep nodes within the fossa ovalis, but avoiding femoral vessel skeletonization.[106,130] Clearly, this technique differs from that described by Catalona, in that the saphenous vein is resected.

In a retrospective review of 60 women with SCC of the vulva who underwent radical vulvectomy and complete ILND with preservation of the fascia lata where all superficial inguinal nodes and deep femoral nodes were removed, 2 of 21 patients with malignant nodes experienced cancer recurrence in the groin. Postoperatively, 13% of patients developed lymphedema and 15% formed lymphoceles (LE 3).[130]

In a review of 93 patients with melanoma of the lower limb who underwent fascia-preserving ilioinguinofemoral lymphadenectomy there was one recurrence (2%) outside the borders of dissection. Transient lower extremity edema occurred in 48% and permanent lower extremity edema occurred in 14% of patients. The authors concluded that preservation of the muscle fascia during LND results in a lower incidence of permanent edema, with no increased risk of recurrence (LE 3).[131]

These studies indicate that the lower incidence of lymphedema after modified (limited) ILND may be related to the smaller extent of the dissection and preservation of the fascia lata, rather than to preservation of the saphenous vein, because in the technique described by Micheletti et al. the saphenous vein is removed.[104-106]

Frozen section

It was originally proposed that modified ILND should be performed with frozen-section examination of the specimen, and if metastases are found, the procedure should be converted to a standard extended ILND (LE 4).[121]

Several authors have proposed that patients with node-negative, high-risk penile cancer should be managed with bilateral superficial or modified ILND with frozen section; complete ilioinguinal lymphadenectomy is then performed if the frozen section results are positive (LE 4).[6,81,84,132,133]

In a study of 26 patients with SCC of the penis who underwent penectomy and bilateral modified ILND with frozen section analysis, the authors concluded that even if frozen section analysis is negative bilaterally, 5.5% of inguinal regions might still harbor occult metastasis (LE 3).[99]

Radical lymphadenectomy

The classic technique of inguinofemoral lymphadenectomy is designed to cover an area outlined superiorly by a line drawn from the superior margin of the external ring to the anterior superior iliac spine, laterally by a line drawn from the anterior superior iliac spine extending 20 cm inferiorly, and medially by a line drawn from the pubic tubercle 15 cm down the medial thigh (Fig. 8).[74,102]

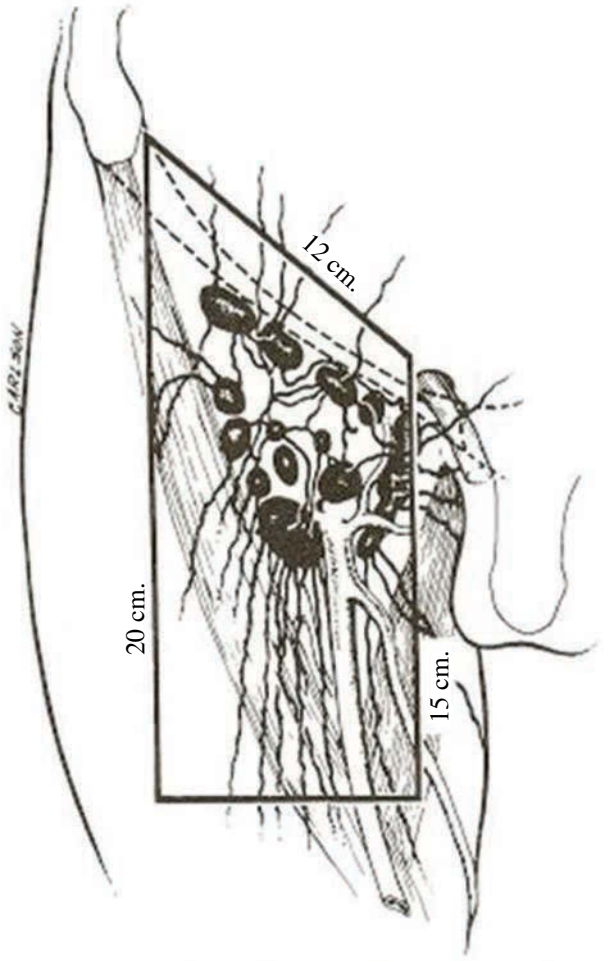

Fig. 8: *Boundaries of the superficial inguinal nodes as described by Daseler (from Johnson DE, Arnes FC – Groin dissection. Chicago , Year Book Medical Publishers, Inc., 1985, pp.15-16).*

Dissection is deepened through the fascia lata overlying the sartorius muscle laterally and the thinner fascia covering the adductor longus muscle medially. At the apex of the femoral triangle, the femoral artery and vein are identified, and the procedure involves skeletonizing the femoral vessels. However, since there are no nodes posterior to the femoral vessels or surrounding the femoral nerve, dissection posterior to the vessels or around the nerve is not necessary. The sartorius muscle is detached from its origin at the anterior superior iliac spine, transposed medially over the femoral vessels and sutured to the inguinal ligament (LE 3).[74,102,130]

Radical ilioinguinal lymphadenectomy is indicated in patients with resectable metastatic adenopathy and may be curative when the disease is limited to the inguinal nodes. It can also be used as a palliative procedure in patients with documented inguinal metastasis who are fit for surgery, in order to prevent subsequent erosion of cancer through the inguinal skin, with foul-smelling drainage or life-threatening femoral hemorrhage (LE 4).[2]

Endoscopic lymphadenectomy

Endoscopic ILND for penile cancer was first proposed by IM Thompson in 2002, and first performed by JT Bishoff et al. in 2003.[134] Video endoscopic inguinal lymphadenectomy (VEIL) has been compared to standard open LND in 15 patients. Complications were observed in 70% of limbs that underwent open surgery and in 20% of limbs that underwent VEIL, while hospitalization was 6.4 days after open dissection and 24 hours after bilateral VEIL (LE 3).[135-138] In another study of endoscopic lymphadenectomy for penile carcinoma (ELPC) in 8 patients lymphoceles developed in three groins (23%) but no wound-related complications were seen (LE 3).[134]

Unilateral or bilateral lymphadenectomy

Because of cross-over drainage of penile structures and normally occurring intercommunications between lymph nodes, bilateral inguinal metastases may occur. Earlier clinical studies showed that in the presence of surgically staged positive nodes on one side, the incidence of positive nodes on the contralateral side varied from 20% to 60% (LE 3).[56] Lymphographic studies have shown that the penis drains to both inguinal sides in at least 12% of cases, whereas lymphoscintigraphy showed bilateral drainage in 60% to 79% (LE 3).[21,139]

The likelihood of bilateral involvement at initial presentation is related to the number of involved nodes in the resected specimen. It has been suggested that with 2 or more metastases the probability of occult contralateral involvement is 30% and warrants early ILND on that side (LE 3).[22] Alternatively, it has been suggested that on

the contralateral inguinal area with no palpable nodes, modified lymphadenectomy can be considered and may be extended if positive nodes are found on frozen section biopsy (LE 3).[140]

It has also been suggested that in patients with unilateral inguinal node metastases at initial presentation of the primary tumor, bilateral ILND should be performed. The contralateral node dissection is limited to the area superficial to the fascia lata and only if frozen section shows histologic evidence of positive superficial nodes is a complete ILND performed (LE 4).[2]

In patients who present with unilateral lymphadenopathy some time after the initial presentation and treatment of the primary tumor, only ipsilateral ILND is necessary (LE 3).[22] Presumably all node metastases will enlarge at the same rate, so bilateral metastases should become palpable at approximately the same time. However, this concept may not apply to all patients with delayed recurrence.

Horenblas et al. noted that in patients with 2 or more unilateral metastases, contralateral occult metastases were noted in 30% of cases. Thus, it has been suggested that in patients with a bulky unilateral recurrence, a contralateral inguinal staging procedure should be considered (LE 3).[2,139] However, the argument that a 30% risk of occult metastasis is an indication for ILND, could be interpreted to mean that all patients except those with a G1T1 primary and nonpalpable nodes should undergo initial prophylactic ILND, because in men with an intermediate risk primary lesion the incidence of inguinal metastases may be more than 30%.

Pelvic lymph node dissection (PLND)

It has been recommended that if tumor is found in the inguinal nodes, bilateral pelvic (iliac) lymph node dissection (PLND) should be performed, because about 30% of these nodes harbor tumor metastases (LE 3).[32]

Overall, the incidence of pelvic node metastases in men with penile SCC is quite low.[9,141] The reported 5-year survival rates in patients with iliac node metastases have ranged from 0 to 66% for all cases, and from 17% to 54% for those with microscopic invasion only, with an estimated average of about 10% (LE 3).[3,7,8,10,22,112,132,142]

In a study of 50 patients the histological grade of the primary tumor was related to the risk of pelvic lymph node metastasis (LE 3).[143] A study of 110 patients showed that the likelihood of spread to the pelvic nodes was related to the number of invaded nodes in the inguinal region, and the authors recommended PLND when 2 or more positive nodes are found in the ILND specimen (LE 3).[43] A study of 78 patients found that important indicators of metastases to the iliac nodes were fixed inguinal nodes larger than 2 cm, as well as palpable iliac nodes (LE 3).[85] It has been proposed that immediate or delayed PLND should be performed in cases where two or more positive inguinal lymph nodes or extracapsular invasion are found on frozen section biopsy or standard pathology examination.[140]

Zhu et al. reported that in men with penile cancer Cloquet's node had a sensitivity of 30% and a specificity of 94% for pelvic node metastases.[144] They found that the risk of pelvic lymph node metastases was significantly associated with the number of positive inguinal nodes, the lymph node ratio (number of positive nodes/total number removed), extranodal extension and the expression of p53 (LE 3).[144] Similarly, in patients with melanoma the tumor status of the Cloquet lymph node was predictive of the tumor status of the iliac lymph nodes (LE 3).[145]

Horenblas stated that patients with only one inguinal node metastasis and no involvement of the most proximal lymph node in the dissection specimen (Cloquet's node) have a very low probability of pelvic node involvement and do not require PLND (LE 3).[22] Lont et al. reported that patients with only 1 or 2 inguinal lymph nodes involved without extracapsular growth and no poorly differentiated tumor within these nodes are at low risk of pelvic lymph node involvement (LE 3).[146]

Earlier authors advocated first doing a limited bilateral PLND before ILND. If the pelvic nodes are negative or not extensively involved, bilateral ILND should be performed, preferably in two

stages (LE 4).[32,58] It has also been suggested that laparoscopic PLND should be performed before ILND.[147] Even in a very recent paper it was recommended that standard PLND as for a radical prostatectomy should be performed before ILND (LE 4).[97]

It has been suggested that if an inguinal node is positive, pelvic CT with FNAC of enlarged pelvic nodes should be performed, because patients with macroscopic lymph node metastases can not be cured by surgery alone and are candidates for adjuvant or neoadjuvant treatment (LE 4).[22] In a study of 33 patients who had undergone ilioinguinal node dissection, CT used for the detection of pelvic node metastases had a sensitivity of 38% and specificity of 100%. More than 3 enlarged inguinal lymph nodes in preoperative CT imaging and lymph node size 3.5 cm in long diameter were prognostic factors for pelvic lymph node metastases (LE 3).[144]

It has been suggested that if extensive pelvic metastases or para-aortic metastases are found, this is a sign of incurability, therefore ILND is not indicated (LE 4).[32,80] If CT shows suspicious inguinal as well as iliac lymph nodes, superficial ILND might be justified on the basis of palliation, but PLND would probably not be beneficial (LE 4).[56] Moreover, it will increase the risk of complications, especially lower limb oedema (LE 3).[95]

Some authors do not attempt *en bloc* removal of the pelvic and inguinal lymph nodes, but simply remove them as separate specimens.[102] PLND can be undertaken simultaneously with ILND, or as a separate procedure. Removal of the nodes through two separate incisions showed the lowest complication rate (LE 3).[9,22]

It has been suggested that the PLND in penile cancer should be more extensive than with staging of prostate or bladder cancer, the rationale being that it is of therapeutic benefit. The proposed boundaries are the ilio-inguinal nerve laterally, the bladder and prostate medially, the common iliac vessels proximally, and the nodes in the obturator fossa and the lymphatic vessels to the groin distally (LE 4).[22]

Complications of lymphadenectomy

Complications after ILND and/or PLND are quite common, but are usually minor and not life-threatening, therefore they may be regarded as a "surgical nuisance" rather than a compelling contra-indication to surgery (Fig. 9).

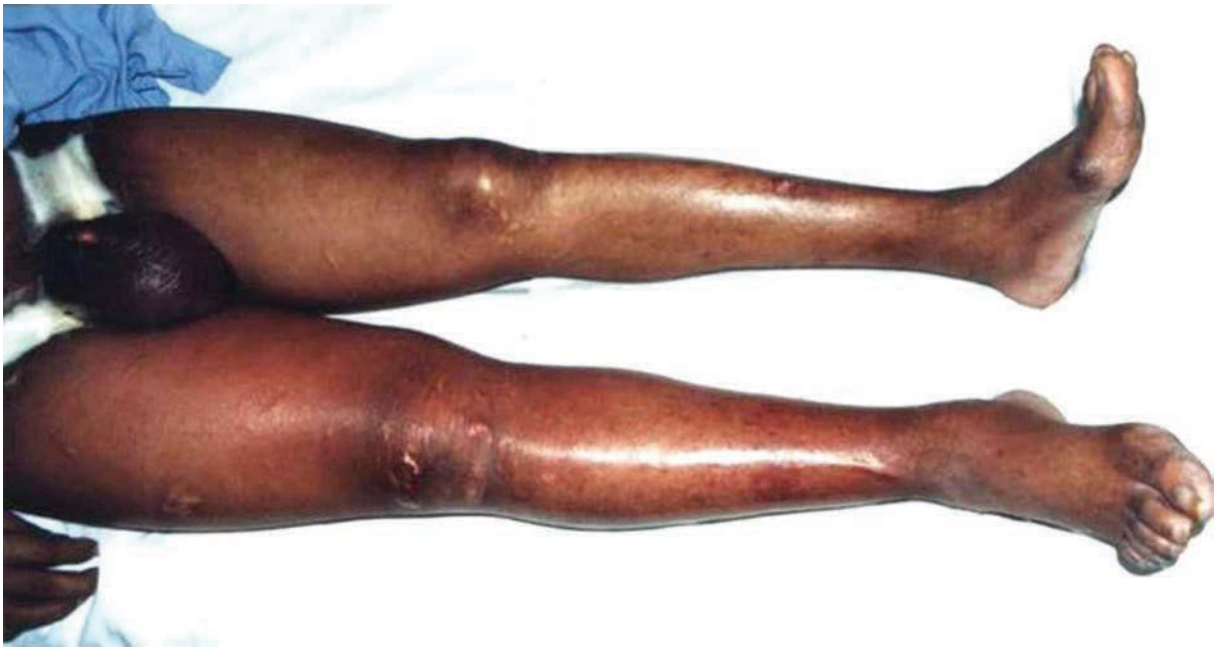

Fig. 9: *Lymphoedema of right leg with acute lymphangitis 7 days after bilateral ILND.*

The reported incidence of complications after lymphadenectomy vary considerably (Table 2). The list below shows the range of reported incidence rates in various studies (LE 3).[1,6,9,22,23,44,94,95,98,109,148-152,155]

1. Flap necrosis / skin edge necrosis: 2.5% to 64%
2. Wound breakdown: 38% to 61%
3. Wound infection: 3% to 70%
4. Seroma: 5% to 87%
5. Lymphocele: 2.5% to 87%
6. Lymphorrhea: 33%
7. Leg lymphedema: 5% to 100%
8. Deep vein thrombosis / thrombophlebitis: 6% to 9%
9. Myocardial infarction: 9%
10. Femoral neuropraxia: 2%
11. Death: 1.3% to 3%
12. Overall: 24% to 100%

In women with invasive SCC of the vulva, the most commonly reported complications of inguinofemoral lymphadenectomy also show wide variations (LE 3).[106]

1. wound breakdown: 8% to 82%
2. wound infection: 9% to 70%
3. lymphocyst: 13% to 87%
4. cellulitis: 6% to 35%
5. lymphedema: 4% to 69%

Reasons for the wide variation in complication rates include the following:[11,151]

1. definition of the complication
2. terminology chosen (wound infection versus cellulitis, seroma versus lymphocele, skin edge necrosis versus wound breakdown)
3. classification (minor, major, early, late)
4. diagnosis (whether by subjective or objective assessment)
5. reporting or recording (whether by surgeon, patient or independent observer)
6. whether complication rates are calculated per patient, per node dissection or as a percentage of total complications (some patients may have several complications)
7. indication for the lymphadenectomy (prophylactic, therapeutic, palliative)
8. extent of the node dissection
9. inguinal radiotherapy before or after the procedure.

Table 2: Chronological summary of the incidence of common complications reported in case series of lymphadenectomy for penile cancer

	Pts (n)	Skin edge necrosis	Wound infection	Seroma	Lymphocele	Lymphedema
Johnson & Lo (1948-83)[5]	67	50%	14%	16%	9%	50%
Darai et al.[156]	85	14%	12%	-	3%	32%
Ravi (1962-90)[149]	112	62%	17%	7%	-	27%
Ornellas et al. (1972-87)[9]	200	45%	15%	6%	-	23%
Bouchot et al. (1960-85)[157]	32	44%	29%	-	-	44%
Ayyappan et al.[85]	78	36%	70%	-	87%	57%
Lopes et al. (1953-85)[11]	145	15%	22%	60%	-	30%
Bevan-Thomas et al. (1989-98)[151]	53	8%	10%	10%	-	23%
Bouchot et al. (1989-2000)[153]	88	-	-	-	-	-
Radical	-	12%	7%	19%	-	22%
Modified	-	3%	1%	3%	-	3%

d'Ancona et al. (1994-99)[99]	26	-	-	-	-	-
Complete	-	38%	-	38%	-	38%
Modified	-	0%	-	26%	-	0%
Kroon et al. (1994-2003)[34]	129	-	-	-	-	-
Radical	-	15%	27%	9%	12%	31%
Sentinel	-	1%	5%	2%	1%	1%
Nelson et al. (1992-2003)[158]	22	10%	8%	-	15%	15%
Pandey et al. (1987-98)[3]	128	20%	17%	16%	-	19%
Perdona et al. (1990-2004)[96]	70	-	-	-	-	-
Bilateral radical	48	8%	8%	13%	4%	21%
Sentinel	22	0%	5%	9%	-	-
Pompeo (1984-97)[49]	50	6%	12%	-	6%	18%
Theron & Heyns (1983-2006)[100]	52	-	-	-	-	-
Deferred	34	21%	35%	-	21%	-
Simultaneous	18	28%	6%	-	44%	11%
Spiess et al.[94]	43	11%	9%	-	2%	17%

- Johnson and Lo: prophylactic = 16, therapeutic = 75, palliative = 10 (+ pelvic = 34)
- Bevan-Thomas et al: prophylactic = 66, therapeutic = 28, palliative = 12 (+ pelvic = 40)
- Nelson et al: prophylactic = 7, therapeutic = 25, palliative = 8 (+ pelvic = 10)
- Pandey et al: synchronous (within 6 months) in 91 patients, metachronous in 37; skin flap used in 60 dissections
- Pompeo: + pelvic nodes = 50
- Spiess et al: diagnostic ILND = 26, therapeutic = 17

Table 2 shows that the reported incidence of complications has decreased somewhat over the past few decades, and that the incidence rates are lower in procedures with a more limited extent of node dissection.

Limiting the extent of surgery (SNB or modified ILND) reduces the incidence of complications (LE 3). In 9 men who underwent modified ILND, early post-operative complications occurred in only four (44%).[123,159] Modified ILND in 10 patients showed early moderate lymphedema in 20% and a transient lymphocele in 30%.[160] In a study of 26 patients who underwent penectomy and bilateral modified ILND at the same operative time with frozen section and complete ipsilateral ILND if the nodes were positive, the complication rates were 39% for modified and 88% for complete ILND.[99] In a retrospective study of 48 patients who underwent prophylactic bilateral radical lymphadenectomy and 22 patients who underwent DSNB the authors concluded that DSNB has lower morbidity.[96]

In a retrospective study of 7 patients who underwent bilateral modified ILND wound infection occurred in one patient, and no major complications occurred.[161] In a study of 140 patients who underwent LND only if sentinel node metastasis was found, complications occurred in 17 of 206 (8%) of the operated groins (in 17 of 140 patients, i.e. in 12%).[33] In a study of DSNB performed in 129 patients, complications occurred in only 14 of 189 (7%) of the node negative groins. All complications of DSNB were minor and easily managed. However, an in-field recurrence after a negative DSNB is perhaps the greatest drawback of the procedure (LE 3).[34]

A retrospective analysis of 23 consecutive patients who underwent SNB did not show any ma-

jor surgical complications (LE 3).[50] DSNB performed in 92 patients between 1994 and 2001 had a complication rate of 10.2% and in 58 patients between 2001 and 2004 the rate of complications dropped to 5.7%. All complications were minor and transient (LE 3).[13] In another study DSNB in 75 patients led to complications in 6 of 143 (4%) groins (in 6 of 75 (8%) patients) (LE 3).[38]

A study of 41 men with SCC of the penis, of whom 22 underwent ILND, showed no significant difference in the complication rates or hospital stay in patients with unilateral compared to bilateral ILND or PLND (LE 3).[158]

Studies of women with SCC of the vulva confirm that limiting the extent of the node dissection reduces the incidence of complications.[162] A retrospective review of 194 women with primary SCC of the vulva showed that age greater than 70, obesity, and extent of lymphadenectomy increased wound breakdown risk. Factors associated with leg edema were: extent of lymphadenectomy, sartorius transposition (lymphedema 55% with and 22% without sartorius transposition), and adjuvant irradiation of groin area (68% with and 34% without adjuvant radiotherapy). Techniques of lymphadenectomy with preservation of the fascia lata and saphenous vein were associated with a decreased risk of postoperative morbidity without jeopardizing outcomes (LE 3).[162] A retrospective study of 29 women with carcinoma of the vulva compared ILND with preservation of the saphenous vein in 18 (37%) groin dissections to 31(63%) in which the saphenous vein was ligated.[163] Complications in the vein-ligated group compared to the vein-spared group were cellulitis in 45% vs. 0%, wound breakdown in 25% versus 0% and chronic lymphedema in 38% versus 11% (LE 3).[163] In a study of 64 women with vulvar malignancies who underwent ILND with sparing of the saphenous vein or ligation of the saphenous vein, transient lymphedema occurred in 44% versus 67%, lower extremity phlebitis in 11% versus 26%, with no difference in the overall 5-year survival rate (LE 3).[164]

Studies of ILND in patients with lower limb melanoma have identified some risk factors for complications. A retrospective study of 212 patients who underwent an ILND for melanoma reported a significant wound complication in 19%.[165] Independent predictors of a major wound complication were BMI and the presence of clinically palpable metastases. Lymphedema occurred in 30% of patients and was significantly associated with clinically palpable nodes containing malignancy (LE 3).[165] In a study of 66 patients with melanoma who had undergone inguinal or ilio-inguinal dissection (9 patients also received postoperative radiotherapy), the incidence of lymphedema varied according to the assessment parameter used, but was 7% to 12% in patients after inguinal dissection compared with 19% to 23% in patients after ilio-inguinal dissection. Radiotherapy increased the risk of lymphedema approximately 13-fold (LE 3).[166]

A systematic review to identify risk factors for seroma formation after breast cancer surgery evaluated 1 meta-analysis, 51 randomized controlled trials, 7 prospective studies and 7 retrospective studies.[167] There was moderate evidence to support a risk for seroma formation in individuals with heavier body weight, extended radical mastectomy as compared with simple mastectomy, and greater drainage volume in the initial 3 days. SNB reduced seroma formation. The following factors did not have a significant influence on seroma formation: duration of drainage; hormone receptor status; immobilization of the shoulder; intensity of negative suction pressure; lymph node status or lymph node positivity; number of drains; number of removed lymph nodes; previous biopsy; removal of drains on the fifth postoperative day versus when daily drainage volume fell to minimal; tumor stage; type of drainage (closed suction versus static drainage); and use of fibrinolysis inhibitor (LE 1).[167]

Preventing complications

It has been suggested that postoperative complications after ILND for penile SCC have been reduced by improved preoperative and postoperative care, advances in surgical technique, including preservation of the dermis, Scarpa's fascia, and saphenous vein, as well as limiting the extent of the dissection and the use of myocutaneous flap coverage where necessary (LE 3).[24]

▪ Antibiotics

Antibiotic therapy for 4-6 weeks following treatment of the primary lesion of the penis has been advised to allow complete resolution of septic lymphadenitis (LE 4).[74,168]

There are no comparative studies on the use of antibiotics, but it seems reasonable to give prophylactic antibiotics at the time of surgery, as this type of surgery should be considered a contaminated procedure, because of the often co-existing inflammatory reaction in the lymph nodes (LE 4).[22]

The specific microorganisms isolated in inguinal wounds include gram negative rods, Staphylococcus species, diphtheroids, and Peptostreptococcus. It has been suggested that proper sterilization of the surgical field prior to the procedure will decrease wound colonization, and that broad-spectrum antibiotics (e.g. ampicillin/gentamycin or ampicillin/ciprofloxacin) prior to skin incision are indicated to decrease the risk of wound infection (LE 4).[94] In patients with pre-operative cellulitis or infection of the inguinal region, bacterial cultures should be obtained and culture-specific oral antibiotics (usually a 1st generation cephalosporin or penicillin) should be given prior to surgical management (LE 4).[94]

It has been suggested that prophylactic antibiotics should be continued for 1 week after surgery, or until all wound drains have been removed (LE 4).[94,97]

▪ Anticoagulation

Heparin may increase the risk of wound hematoma and serous wound drainage due to continued extravasation of lymph.[168] In a study of 44 patients with melanoma undergoing ILND, heparin 5000 units subcutaneously 2 hours prior to and every 8 hours after operation was used.[169] The overall incidence of deep vein thrombosis (DVT) was 13.6%. Heparin did not reduce the DVT incidence, but the total volume and duration of wound drainage was significantly greater in the group treated with low-dose heparin (LE 2).[169]

There seems to be a trend toward avoidance of prophylactic low-dose heparin because of the possibility of an increased risk of lymphocele formation (LE 3).[97,158,170] However, some authors still advocate using routine low-molecular weight heparin, starting the evening before surgery and continuing while the patient is on bedrest (LE 4).[22,94] It has been proposed that among patients with a remote history of DVT, peri-operative low-dose low-molecular weight heparin should be utilized until post-operative day 28. In patients with a history of DVT or pulmonary embolism (PE) in the preceding 6 months, therapeutic dose anticoagulation using low-molecular weight heparin should be restarted when the risk of postoperative hemorrhage is minimal, with subsequent conversion to oral warfarin as indicated (LE 4).[94]

The use of antiembolic stockings or intermittent compression devices immediately prior to anesthetic induction to prevent venous stasis has also been recommended (LE 4).[74,94]

▪ Bowel cleansing

It has been suggested that a low-residue diet on the day before surgery and a cleansing enema or 24-hour bowel preparation with Golytely will minimize the risk of wound contamination (LE 4).[74,108] However, there is no evidence of any benefit, and bowel preparation can not be routinely recommended.

▪ Skin incision, mobilization and closure

The blood vessels supplying the skin of the inguinal regions are superficial branches of the inferior epigastric, external pudendal and circumflex iliac arteries. The blood vessels course in the fatty or superficial layer of the superficial fascia and run parallel to the inguinal ligament. All three of these vessels are transected during the course of ILND, and the flaps must rely on anastomotic branches and the microcirculation in the flaps. These branches lie in Camper's fascia and tend to parallel the natural skin crease and the inguinal ligament.[22,74,94,102,108,168,171]

Several authors have suggested that it is important to make incisions parallel to the inguinal ligament to minimize the risk of flap necrosis. Sraight vertical and S-shaped incisions cut across the anastomotic vessels in Camper's fascia. Fur-

thermore, postoperative swelling of the thigh puts traction on these incisions. Most authors recommend a horizontal incision placed just below the inguinal ligament that follows the natural skin lines (LE 3) (Fig. 10).[22,74,94,102,108,168,171]

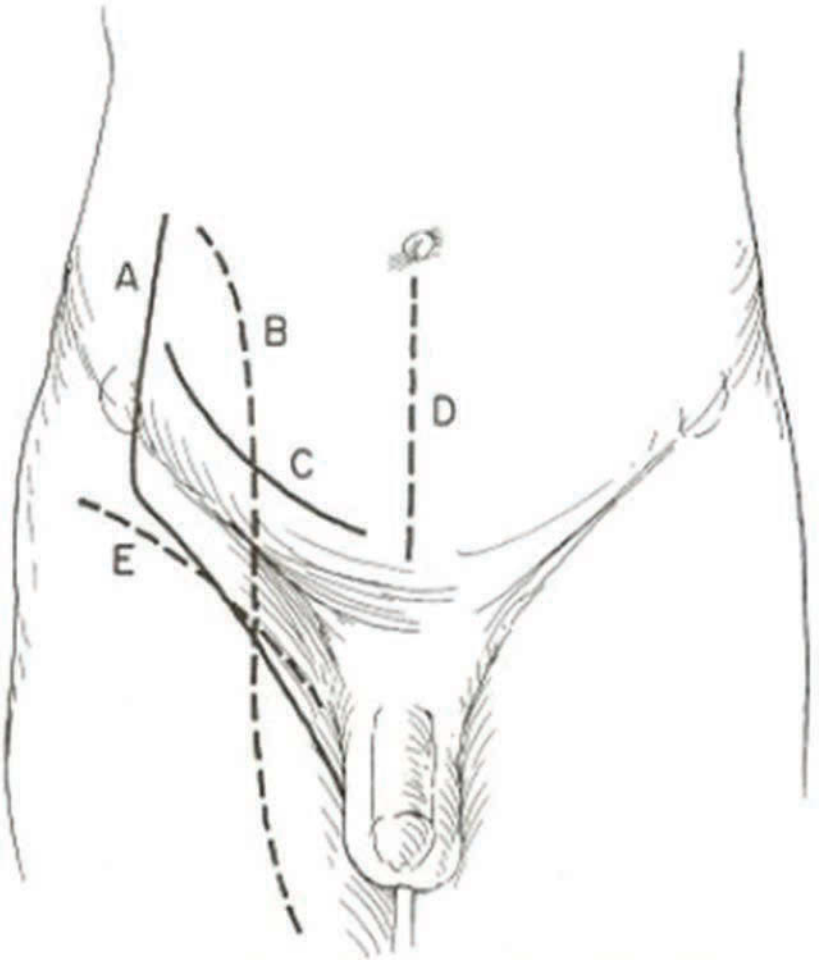

Fig. 10: *Different skin incisions used for ILND and PLND[74] (from Das S, Crawford ED: Carcinoma of the penis. In Crawford ED, Das S (eds). Current Genitourinary Cancer Surgery, Philadelphia, Lea & Febiger, 1990, p.376).*

A study of 50 ILNDs indicated that the optimal surgical approach is an elliptical incision removing a 4 cm width of skin over the inguinal nodes (LE 3).[172] A more recent review of 25 patients who underwent ILND concluded that an elliptical incision orientated as a long oblique of at least 4 cm width, compared to a similarly oriented incision with no skin excision, had significantly fewer complications and shorter hospital stay (LE 3).[173]

A non-randomized study compared 3 types of incision: (1) a large bi-iliac incision, (2) a transverse S-shaped incision and (3) a skin-bridge technique with two separate incisions.[9] The latter had the lowest percentage of skin necrosis and the least lymphoedema (LE 3).[9] Another study reported that the incidence of flap necrosis was highest using a T shaped incision when compared to either horizontal or straight incisions (LE 3).[149] A study of 20 consecutive patients who underwent 25 groin dissections indicated that S-shaped incisions more often resulted in wound infection and lymphedema than straight incisions (LE 3).[174]

If there are large inguinal lymph nodes involving the skin, or if FNAC was positive, the oblique skin incision can be easily modified to circumscribe this skin and remove it *en bloc* with the node-bearing tissue.[108] It has been suggested that the oblique incision also permits easy access for PLND. The external oblique aponeurosis is incised in line with its fibers at the upper margin of the external inguinal ring, and the obliquus internus and transversus abdominis muscles are retracted or divided to gain access for PLND (LE 4).[108]

In a recent description of surgical technique, Loughlin advocated the use of three parallel vertical incisions, stating that he had encountered no problems with crossing the inguinal crease, and that the vertical groin incisions afford better exposure superiorly (LE 3).[97]

It is self-evident that skin flaps which are too thin are at increased risk of ischemia, skin necrosis and wound dehiscence.[94] It has been suggested that the subcutaneous tissue superficial to the fibrous layer of Camper's fascia, which does not contain lymph nodes, should be preserved (LE 4).[32,168] Alternatively, it has been suggested that thick skin flaps should be developed below Scarpa's fascia (LE 4).[94] Meticulous atraumatic tissue handling throughout surgery may reduce the risk of wound-related problems (LE 4).[94]

It has been suggested that excess skin should be excised prior to closure, and that the subcutaneous tissue can be anchored to the underlying muscles with interrupted absorbable sutures to eliminate dead space and prevent fluid collection in the wound (LE 4).[74,108]

Inguinal reconstruction with myocutaneous flaps when required can speed up wound healing and avoid wound dehiscence related to excessive tension (LE 4).[94]

▪ Fluorescein

Intravenous fluorescein (10 ml) injection and observation of the skin flaps 15 minutes later under Wood's (ultraviolet) light can be used to demonstrate blood supply to skin flaps.[175] Poorly vascularized areas appear blue, while areas with good viability exhibit a yellow/green fluorescence.[102] The procedure has found limited clinical application, probably because of the required additional operative time and concern over adverse drug reactions, including acute myocardial infarction and pulmonary edema (LE 4).[5]

▪ DMSO

A randomized, prospective study on the effect of dimethylsulfoxide (DMSO) on skin flap viability in patients undergoing mastectomy and axillary lymph node dissection included 24 who had topical 60% DMSO applied to their flaps every 4 hours for 10 days after operation and 27 who had operations alone. The authors concluded that topical application of DMSO reduced skin flap ischemia.[176] In a prospective, randomized study of 66 patients with breast cancer who had skin flaps created during mastectomy, topical application of DMSO reduced skin flap necrosis (LE 2).[177] However, this technique has not been evaluated in ILND for SCC of the penis.

▪ Lymph duct ligation

It has been suggested that lymphorrhea and seroma can be prevented by careful ligation of lymphatics (LE 4).[102] Lymphatic vessels and channels can be ligated with small, absorbable sutures, titanium surgical clips, or using the Ligasure® device or Harmonic scalpel®. In the breast cancer literature, neither of these devices has been shown to reduce seroma formation or increase cost-effectiveness, but they have not been evaluated prospectively in ILND (LE 3).[94,171]

A study of electrodiathermy or ultrasonic sealing of lymphatics concluded that it could reduce the complication rate and operating time of conventional ilioinguinal node dissection (LE 3).[178]

In one study lympho-venous anastomoses (LVA) were performed in 30 patients immediately after the completion of ilio-inguinal dissection for metastatic node involvement and the results were compared to a historical control group of 84 patients.[179] Local-regional complications occurred in 38% versus 66%, leg lymphedema occurred in 30% versus 75%, and hospital stay was 18.5 versus 34.7 days. The authors suggested that LVA should be routinely used following ilio-inguinal node dissections (LE 3).[179]

▪ Sartorius transposition

Earlier articles stated that the blood supply of the sartorius muscle enters it approximately 10 cm distal to its origin.[102] A more recent study found that the proximal pedicle of the sartorius muscle is consistently located 6.5 cm from the anterior superior iliac spine and that preservation of the proximal pedicle during dissection ensures viability of the sartorius

muscle transposition flap for the treatment of complex groin wounds (LE 3) (Fig. 11).[180]

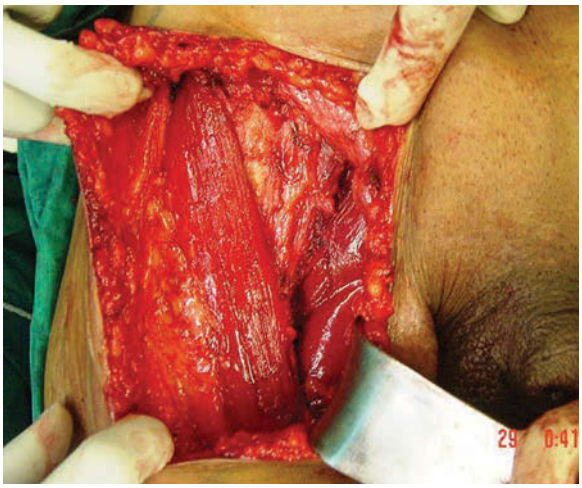

Fig. 11: *Sartorius muscle exposed prior to transposition to cover femoral vessels.*

Another recent study found that the sartorius muscle can be divided into as many as five arterial and nervous segments. In the proximal and middle parts, the muscle has better arterial supply. The segments can be filled by adjacent pedicles, due to an elongated net of anastomoses, which allows a longer arc of rotation in the construction of pedicled flaps (LE 3).[181]

A study of 10 patients used transposition of the sartorius muscle and fibrin glue without a suction drain, and reported lymphocele formation in 33%, but no necrosis of the skin edges, subcutaneous infection or lymphorrhea (LE 3).[182]

A study of 101 women with vulvar cancer who underwent ILND concluded that sartorius muscle transposition significantly reduced the incidence of wound morbidity.[183] A prospective, randomized trial of sartorius transposition in 61 women with SCC of the vulva undergoing ILND found no statistically significant differences in the incidence of wound cellulitis, wound breakdown, lymphedema, or rehospitalization.[184] The incidence of lymphocyst formation was increased in the sartorius transposition group, but after adjusting for age the groups appeared similar. The authors concluded that sartorius transposition after ILND does not reduce postoperative wound morbidity (LE 2).[184]

A retrospective study of 28 consecutive patients undergoing ILND for melanoma metastases found that transposition of the sartorius muscle was not associated with reduced lymph drainage time. A two-staged approach, with initial sentinel lymph node resection and ILND in a second operation, led to shortened duration of lymph leakage. Prolonged lymph drainage was more frequent in older, obese patients affected by diabetes mellitus and hypertension (LE 3).[185]

▪ Flaps

Various flaps can be used to cover tissue defects after radical ILND (LE 3):

1. scrotal skin[186,187]
2. gracilis myocutaneous flap[188]
3. tensor fascia lata myocutaneous flap[189,190,191]
4. internal oblique muscle as a transposition flap based on the ascending branch of the deep circumflex iliac artery[192]
5. deep inferior epigastric artery based rectus abdominis myocutaneous flap[188,189,190]
6. spermatic cord.[191]

It has been suggested that, where skin edges do not approximate, the margins of the skin flaps should be sutured to the underlying muscle with interrupted absorbable sutures, and the muscle not covered primarily by skin flap can then be covered by a split-thickness skin graft (LE 4).[108]

A case report has described primary closure of a large skin defect after ILND with the aid of a skin stretching device (Sure-Closure) which allows the skin to be stretched beyond its inherent extensibility (LE 4).[193]

▪ Drains

The term ‘seroma’ is derived from the assumption that the fluid is a filtrate of plasma. It can be a protein-poor transudate, or a protein-rich exudate due to increased capillary permeability, characteristically observed during the inflammatory phase of wound healing.

It has been suggested that lymphorrhea and seroma can be prevented by postoperative suc-

tion drainage, and that the drains should be removed when the 24-hour output becomes less than 30-50 ml, usually 3-17 days postoperatvely (LE 4)[74,94,102,108,171,194] Migration of bacteria along these drains may increase the risk of infection if the drains stay *in situ* for a long time (LE 4).[194]

There is a theoretical risk that the presence of a suction drain may prolong and intensify the inflammatory phase, and may also prevent leaking lymphatics from closing, thus facilitating seroma formation (LE 4).[194,195]

A prospective randomized trial in women undergoing axillary dissection for breast cancer randomized patients between a high (n = 73) or a low vacuum (n = 68) drainage system. The volume of drainage, duration of seroma production, number of wound complications or infections did not differ significantly between the groups. There was a significant positive relationship between body mass index and seroma production, independent of the drainage system (LE 1).[196] A prospective randomized study comparing half negative suction and full vacuum suction drainage in patients following modified radical mastectomy showed no significant difference in the incidence of seroma formation in the two groups, but half vacuum suction drains were removed earlier and had a significant reduction in hospital stay (LE 1).[194]

In a prospective randomized study of 116 patients undergoing surgery for breast cancer, drains did not prevent seroma formation, and were associated with higher pain scores and longer postoperative stay (LE 1).[195]

- **Fibrin sealant**

The use of fibrin glue is aimed at sealing 'leaky' capillaries and suppressing dead spaces that may produce hematomas, subcutaneous infection or lymphoceles, and at avoiding the use of an aspiration drain, which may cause or contribute to persistent lymphorrhea (LE 4).[182,195]

In a study of modified ILND procedures, use of a vaporized tissue sealant when closing the wound without a suction drain led to only 3 seromas among 118 procedures.[94]

A randomized study of 150 women with vulvar malignancy undergoing ILND compared sutured closure to fibrin sealant sprayed into the groin followed by sutured closure. There was no statistically significant difference in overall complications, lymphedema, duration or volume of drainage, incidence of inguinal infection, wound breakdown or seroma. There was an increased incidence of vulvar infections in the fibrin sealant arm. The utilization of a drain was associated with an increase in vulvar and inguinal wound breakdown (LE 1).[197]

A prospective randomized trial of 48 melanoma patients concluded that intraoperative application of a fibrin sealant following ILND did not reduce the time to drain removal or postoperative morbidity (LE 1).[198]

A prospective randomized trial in 108 breast cancer patients who underwent axillary lymphadenectomy concluded that fibrin glue reduced postoperative drainage and hospital stay, but did not affect delayed seroma formation (LE 1).[199] A randomized study of women undergoing lumpectomy or modified radical mastectomy for breast cancer showed that fibrin sealant at the axillary dissection site significantly decreased the duration and quantity of serosanguinous drainage (LE 1).[200] A study of 26 patients who underwent total or modified radical mastectomy found that the intraoperative application of fibrin sealant reduced serosanguinous drainage and may allow earlier removal of closed suction drainage catheters (LE 1).[201] In a prospective randomized study of 116 patients undergoing surgery for breast cancer, the use of fibrin sealant without a drain reduced the incidence and total volume of seroma (LE 1).[195] However, a review of 11 randomized controlled trials to study the efficacy of fibrin sealants in breast cancer surgery concluded that fibrin sealant did not reduce the rate of postoperative seroma, the volume of drainage, or the length of hospital stay (LE 1).[202]

A randomized study of 58 patients with axillary lymph node metastases of malignant melanoma who underwent radical axillary LND for metastatic malignant melanoma concluded that fibrin glue intraoperatively did not decrease lymphatic leakage (LE 1).[203] In a randomized study of 50

patients undergoing axillary lymphadenectomy fibrin glue spray and a collagen patch in addition to suction drainage did not always prevent seroma formation, but did reduce seroma magnitude and duration (LE 1).[204]

- **Dressings**

It has been suggested that the wound should be made as airtight as possible, because suction catheters are used routinely for drainage, and the application of pressure by heavy dressings on the thin flaps is to be avoided (LE 4).[108]

A prospective, randomized study of 150 women undergoing axillary LND for breast cancer concluded that a compression axillary dressing compared to a standard dressing did not decrease postoperative drainage and may increase the incidence of seroma formation after drain removal.[205]

- **Immobilization**

It has been suggested that after ILND for penile cancer the patient should be maintained on bedrest for 7 days, with both legs elevated (LE 4).[74,102] Lymph flow increases with motion in the lower limb, whereas immobilization permits the regeneration of lymphatics or the opening of anastomotic lymphatics. It has been suggested that the extremity must never be permitted to become dependent or active until the inguinal incision has healed with no residual fluid beneath the flaps (LE 4).[108]

However, most recent papers recommend early or immediate ambulation after ILND (LE 4).[22,97,158,170,171] If a myocutaneous flap has been used, mobilization should be avoided in the early post-operative period (48–72 hours) to avoid compromising the blood supply to the flap (LE 4).[94]

- **Compressive stockings**

Efforts to minimize lower extremity lymphedema include early ambulation, the use of elastic stockings and sequential compression devices (LE 4).[158,170] It is advised that individually fitted elastic stockings should be worn for at least a 6 months after surgery (LE 4).[22,94,97]

- **Preventing neuropraxia**

Neuropraxia and nerve injury are very rare (2%), but can result from transection, traction, or heat transmission to the femoral nerve or other peripheral nerves. During intra-operative placement of retractors, great care should be taken to avoid excess traction on peripheral nerves (LE 4).[94]

- **Catheterization**

Catheterization with all aseptic and antiseptic precautions should be performed in the operating room after the patient is anesthetized, to monitor intraoperative urinary output and to keep the bladder empty if PLND is performed. It has been suggested that the need to keep the wounds dry of urine require that the catheter be left in place as long as the patient is confined to bed postoperatively (LE 4).[108]

- **Referral of patients**

It has been suggested that extensive experience in lymph node dissection is an important factor in preventing complications, thus it is reasonable to refer patients to institutes with a large experience (LE 4).[9,22]

Treating complications

Lymphoedema treatment can be divided into three main approaches: physical therapy, drug therapy, and surgery, all of which are supplemented by patient education.[206-208]

1. Preventive aspects: making patients aware of the factors that exacerbate their condition
2. Physical therapy. to control lymph formation and improve lymph drainage
   - 2.1 Elevation of the affected limb above the level of the heart
   - 2.2 Exercise
   - 2.3 External limb compression: bandaging, compression garments and static compression devices, pneumatic compression
   - 2.4 Massage
   - 2.5 Decongestive lymphatic therapy

(DLT): this combines four physical therapy methods: gentle massage therapy of superficial lymphatics, skin care, compression bandaging and exercise

3. Drug therapy
   - 3.1 Benzopyrones
   - 3.2 Diuretics
4. Surgical treatment:
   - 4.1 Lymphovenous anastomosis and lymphatic reconstruction using microsurgical techniques
   - 4.2 Liposuction (mainly reported for upper extremity oedema)
   - 4.3 Limb-reducing operations (radical excision of the oedematous skin and epifascial compartment, and split-thickness skin grafting).

Lymphoceles or seromata may be treated in the outpatient clinic by regular percutaneous aspiration, or the instillation of sclerosants such as povidone iodine, talcum powder, or doxycycline (LE 4).[171,209] A case of recurrent inguinal lymphocele formation after ILND was treated by lymphographic mapping and selective occlusion of the lymphatic vessels with titanium clips (LE 4).[209]

Vacuum-assisted closure (VAC) was used in 4 of 8 patients who underwent lymphadenectomy and resulted in shortened hospitalization and reduced overall costs (LE 3).[210] VAC therapy has been reported to be contraindicated in the presence of necrotic tissue, open fistulas, and untreated osteomyelitis; it is also not approved for use in the presence of malignancy in the wound. In a study of 6 patients with inguinal wounds following ILND for penile cancer no local recurrence in the VAC group was noted despite positive lymph nodes (LE 3).[211]

Radiotherapy

Ekstrom and Edsmyr reported a series of 130 patients with clinically impalpable nodes treated with adjuvant radiation therapy (RT), in which 29 of 130 (22%) men subsequently developed inguinal metastases (LE 3).[77] Murrell and Williams found that 3 of 11 patients (25%) with non-palpable nodes who received RT to the inguinal area subsequently developed inguinal metastases (LE 3).[212] These percentages are similar to the incidence of metastases found in histological examination of clinically non-palpable nodes, suggesting that RT did not alter the course of the disease.

RT for inguinal metastases documented by histologic examination has been compared with surgery for the node-positive groin. The 5-year survival rate was 50% in the surgically treated group and 25% in the irradiated group (LE 3).[213] This indicates that RT to the inguinal areas is not therapeutically effective.[212,214]

The controversy over RT for inguinal node metastases concerns the fact that staging is not always peformed. Narayana et al. reported that after inguinal RT death due to penile cancer occurred in 11 of 16 (69%) patients with histologically positive nodes and in 18 of 30 (60%) patients with unknown inguinal histology. In patients with histologically proven carcinoma death due to penile cancer occurred in 11 of 16 (69%) after RT and in 17 of 31 (55%) after LND only (LE 3).[79]

In a small series the 5-year survival after ILND was 67%, compared with 25% for irradiated patients.[215]

A study of 63 patients with penile carcinoma and 13 with carcinoma of the urethra suggested that prophylactic irradiation of regional lymph nodes should be performed in all tumors with more than T2 extension and in tumors located at the base of the penis (LE 3).[216]

In a study of 64 patients with penile cancer treated with combined surgery and RT, the lymph nodes received doses of 45 to 55 Gy. In case of demonstrated lymph node invasion, local control was achieved in 14 of 19 cases (74%). Among patients who developed recurrences during the first 2 years, not one could be cured in the long run (LE 3).[217]

In a study of 201 patients, of whom 106 had clinically metastatic inguinal lymphadenopathy, patients with inguinal nodes larger than 4 cm received 40 Gy RT before undergoing node dissection. Perinodal infiltration, thought to have an adverse

impact on survival, was found in 14 of 43 nonirradiated groins (33%) but in only 3 of 34 irradiated groins (9%). Subsequently, there was a statistically significant difference in groin recurrences, i.e. 3% versus 19% in the radiated and unirradiated groups (LE 3).[10,218] This appears to show that RT does have some effect in patients with large metastatic nodes and extranodal infiltration.

In a study of 66 patients who presented with nonsuspicious nodes, 57 were placed on a surveillance program, while LND was performed in 5 (with adjuvant external RT in 1) and 4 were treated with RT only. The management of 40 other patients with clinically suspected nodes included surveillance in 5, LND in 27 (with adjuvant RT in 11), biopsy in 4 and RT in 4. Postoperative RT was given if more than 2 nodes were involved or when extracapsular growth was observed. Overall, 25 patients had a regional recurrence (25 of 70 irradiated patients = 36%) only 5 of whom (20%) could be cured subsequently (LE 3).[43]

A study of 156 patients, where RT was administered to 120 with inguinal lymph node involvement and 9 with distant metastases, concluded that pre-operative inguinal RT was useful in patients with mobile groin nodes ≥4 cm in size. Pelvic and/or para-aortic RT was ineffective in patients with pelvic node metastases.[218]

In a prospective nonrandomized study of 64 patients with carcinoma of the penis and clinically negative nodes (N0, N1-2a), management with bilateral ILND, RT to the groin or surveillance led to overall 5-year survival rates of 74%, 66% and 63%, respectively.[64] N0 patients had a statistically significantly higher survival rate in the bilateral ILND group when compared with the others. During follow-up relapses occurred in 10 (15%) patients: 7, 2 and 1 in the surveillance, RT and bilateral ILND groups, respectively, and all relapses ended fatally.[64]

In a retrospective study of 40 patients with penile SCC the regional failure rates after ILND for pathological inguinal lymph node metastases were 11% (1/9) and 60% (3/5) in patients with and without adjuvant RT. The authors concluded that for patients with pathologically positive inguinal lymph node metastasis, adjuvant RT can increase inguinal control.[219]

Mistry et al. reported a study of men with SCC of the penis where lymph node recurrence occurred in 11/47 (23%) on surveillance, in 3/7 (43%) after LND only, and in 2/4 (50%) after RT only. Death due to penile cancer occurred in 8 (17%), 2 (29%) and 3 (75%) of the groups, respectively (LE 3).[91]

A report of 50 patients with cancer of the penis, where node positive patients underwent bilateral removal and subsequent irradiation, concluded that this leads to bilateral edema of the lower limbs in a high percentage of cases (LE 3).[220] It is generally accepted that irradiation of the groins makes them more difficult to evaluate for the development of metastases and has adverse effects on wound healing if subsequent ILND is required (LE 4).[168] A study of 231 inguinal and 174 ilio-inguinal lymphadenectomies performed on 234 patients with penile carcinoma concluded that pre-operative radiation to the groin significantly increased the healing complications (LE 3).[149] The combination of ILND and RT causes additional sclerosis of lymphatics and deters lymphatic regeneration, greatly increasing the risk of lymphedema (LE 4).[108]

Experience in the use of RT for the treatment of the inguinal nodes in women with SCC of the vulva may provide an important parallel, although the findings can not be directly extrapolated to SCC of the penis.

In women with SCC of the vulva, a retrospective study comparing inguinofemoral RT (n = 23) to ILND (n = 25) for cN0-1 patients suggested that RT is a viable alternative to groin dissection. The node control rates and 3-year cause specific survivals were not signficantly different, but the morbidity of ILND was greater than that of RT (LE 3).[221]

In a study of 135 patients with invasive vulvar carcinoma without clinical evidence of inguinal lymph node involvement (T1 N0-1) 65 patients received postoperative inguinofemoral RT, and 70 did not.[222] The 5-year survival rates were 94% and 91%, respectively. There were no statistically significant differences in inguinal relapse (4.6% versus 10%) or complication rates (7.7% versus

2.9%) between the irradiated versus nonirradiated groups. The authors suggested that inguinal RT may not be necessary in low-risk cases (G1-2 T1 N0-1, no central location, no vessel invasion, tumor thickness ~2 mm) (LE 3).[222]

A review of 3 papers comparing ILND to inguinal RT in women with SCC of the vulva concluded that the incidence of groin recurrences after primary RT was higher and survival was worse compared with surgery. Morbidity after primary RT was lower compared with surgery. Although the technique of RT could be criticized, other uncontrolled data did not give evidence for a similar or better groin control for RT when compared to surgery. The authors suggested that surgery remains the cornerstone of therapy for the groin nodes in women with vulvar cancer, but that patients not fit enough to withstand surgery can be treated with primary RT (LE 3).[223]

In a retrospective study of 227 women with SCC of the vulva the inguinal nodes were clinically suspicious in 67 patients and clinically negative in 160. LND alone was performed in 119 patients, LND plus RT in 57, and RT alone in 51. The 5-year inguinal node recurrence rates were similar for the three groups (16%, 13%, and 16%, respectively). The authors concluded that RT alone or in combination with LND is highly effective in preventing node recurrence in patients with SCC of the vulva and is associated with a low risk of major late complications (LE 3).[224]

A retrospective study of 40 patients with SCC of the vulva and clinically involved inguinal nodes treated either by full ILND or by debulking of the involved inguinal lymph nodes followed by RT showed no difference in groin recurrence rates between the groups. The study showed that nodal debulking, when compared with full ILND, did not jeopardize survival when both were followed by groin and pelvic radiation.[225]

A retrospective review of 194 patients with primary SCC of the vulva showed that adjuvant inguinal RT was a risk factor for chronic leg edema (68% with and 34% without adjuvant RT) (LE 3).[162]

From data of patients with SCC in the head and neck region, adjuvant postoperative RT is advised in patients with extensive metastases and/or extranodal spread.[226] However, some reports suggest that this strategy should possibly be replaced by adjuvant chemotherapy.[227]

It has been suggested that prophylactic inguinal RT in clinically node-negative men with SCC of the penis is not advisable, for the following reasons (LE 4):[22]

1. most patients will not benefit (because they do not have node metastases), the argument being the same as for prophylactic ILND
2. all patients will be exposed to the potential complications of RT, e.g. epidermiolysis or lymphoedema and fibrosis
3. follow-up is more complicated because of the fibrotic changes, making physical examination unreliable
4. data indicate a similar recurrence rate in series where radiation was compared with surveillance.

It has been suggested that, based on experience in head and neck surgery, adjuvant RT should be given to patients with two or more node metastases, extracapsular growth and pelvic metastases (LE 4).[22]

Chemotherapy

A study of 204 patients with penile cancer and 14 patients with recurrence in the inguinal nodes reported a relapse rate of 45% in patients treated only surgically, versus 16% in those who received adjuvant chemotherapy after surgery. The authors concluded that adjuvant chemotherapy can improve the results of radical surgery significantly (LE 3).[228] However, analysis of the data showed that those patients most in need of adjuvant treatment (bilateral metastases, pelvic involvement) fared worst.[22]

In a study of 13 patients with radically resected node metastases treated with adjuvant chemotherapy, 3 of 8 patients were cured, 4 progressed, while one died from chemotherapy related pulmonary toxicity. The authors concluded that adjuvant chemotherapy can increase survival compared to surgery alone, but that the risk of toxicity is high (LE 3).[229]

A literature review showed that after ILND the 5-year survival for men with negative inguinal nodes is 93% to 100%, for those with one positive node or unilaterally positive nodes it is around 80%, for ≥2 unilaterally positive nodes it is about 50%, and for bilaterally positive nodes, extranodal extension or positive pelvic nodes it is approximately 10%.[73,132]

It has been suggested that adjuvant therapy is advisable when there are two or more positive nodes, extranodal extension of cancer or pelvic node metastasis (LE 3).[2,140] However, relapses after adjuvant chemotherapy have occurred only in patients with bilateral and/or pelvic metastases, therefore the results of chemotherapy for extensively metastatic penile SCC are not very good.[140,228,230]

Follow-up

Previous studies noted that after treatment of the primary penile lesion most metastases occur in the first 6 to 12 months,[231] 18 months,[10] 2 years,[43,99] or 3 years,[220] but may occur after 5 years,[232] 10 years[233] or 25 years.[92,93,231]

Based on other proposed follow-up protocols in the literature, the following protocol is suggested (Table 3) (LE 3):[2,232]

Table 3: Follow-up protocol for men with penile SCC

	Monthly interval			
	Year 1-2	**Year 3**	**Year 4**	**Year 5**
Low-risk primary lesion: G1-2, Tis, Ta, T1, no vascular invasion	3	4	6	12
High-risk primary: G3, T2-3, vascular invasion	2	3	6	12
Penile preserving treatment	3	6		
Partial penectomy	6	12		
Pathologically N0 (at SNB)	4	6	12	12
Pathologicaly N1 (at SNB)	3 **	4 **	6 **	12 **

** includes: Ultrasound with fine needle aspiration cytology (US-FNAC)
Computed tomography (CT)
Chest X-ray (CXR)

Recommendations

1. Fine needle aspiration cytology should be performed in all patients with palpable nodes (under ultrasound guidance in those with nonpalpable nodes), because if it is positive, therapeutic rather than diagnostic lymphadenectomy can be performed (GR B).
2. Antibiotic treatment for 3-6 weeks in patients with palpable inguinal nodes is not recommended, because it is not useful in determining whether the nodes contain metastases, and will not substantially influence management choices (GR B).
3. Abdominopelvic CT and MRI are not useful in patients with nonpalpable nodes, but may be used in those with large, palpable inguinal nodes to determine the presence of gross pelvic or distant metastases, which may indicate the need for neoadjuvant chemotherapy prior to surgery (GR B).
4. The statistical probability of inguinal micrometastases can be estimated using risk group stratification or a risk calculation nomogram, provided histopathological assessment of the complete primary lesion is available, not just a biopsy specimen (GR B).
5. Surveillance of the inguinal regions is recommended if the probability of positive nodes on the nomogram is less than 0.1

(10%), alternatively if the primary lesion is G1, pTis, pTa (verrucous carcinoma) or pT1 and cN0 with no lymphovascular invasion, provided that (1) the patient is willing to comply with regular follow-up, and (2) obesity, prior inguinal surgery or radiotherapy do not prevent clinical assessment of the groins (GR B).

6. In socio-economic or other circumstances which may prevent regular follow-up or seriously impede reliable surveillance, prophylactic inguinal lymph node dissection (ILND) may be a preferable option, despite the level of morbidity (GR C).
7. In the intermediate risk group (nomogram probability 0.1 to 0.5 (10% to 50%) or primary tumor G1-2, T1-2, cN0, no lymphovascular invasion), 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. If not, sentinel node biopsy (SNB) (conventional or dynamic) or limited (modified) ILND should be performed (GR B).
8. In the high-risk group (nomogram probability more than 0.5 (50%) or primary tumor G2-3 or T2-4 or cN1-2, or with lymphovascular invasion), 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 (GR B).
9. It is not necessary to wait for 2-6 weeks after penectomy before performing ILND, because modified (limited) or radical (complete) ILND can be performed at the same time as penectomy without an increased risk of complications (GR C).
10. Inguinal sentinel node biopsy (SNB) based on anatomical position (as described by Cabanas) may be performed, provided the patient is willing to accept the risk of a false-negative rate of up to 25%, because the complications are less than for complete ILND (GR C).
11. Dynamic sentinel node biopsy (DSNB) with lymphoscintigraphic localization can be performed if the technology and expertise are available, although considerable experience is necessary to reduce the false-negative rate below that of conventional SNB (GR C).
12. Modified ILND with limited, medial dissection and conservation of the saphenous vein and fascia lata may be performed instead of complete (radical) ILND in order to reduce the complication rate, although the false-negative rate may be similar to that of anatomical SNB (GR C).
13. Frozen section histopathology can be used during SNB or modified ILND with the objective of immediately proceeding to complete ILND if the frozen section is positive, although there are no data about the sensitivity or specificity of frozen section in this situation (GR C).
14. In patients with cyto- or histologically proven inguinal node metastases which are considered to be surgically resectable, a complete ILND should be performed ipsilaterally, because this may be curative (GR B).
15. In patients with inguinal node metastases involving 2 or more nodes on one side, contralateral limited ILND with frozen section should be performed, and complete ILND if the frozen section is positive (GR B).
16. If clinically enlarged and suspicious inguinal nodes are detected during surveillance, complete ILND should be performed on that side only (GR B), and SNB or limited ILND with frozen section on the contralateral side can be considered (GR C).
17. Endoscopic ILND requires further study to show whether it can reduce complication rates without decreasing long-term survival rates (GR C).
18. Pelvic (iliac) lymphadenectomy (PLND) is recommended if there are 2 or more inguinal nodes with proven metastases, or grade 3 tumor in the nodes, or extracapsular extension of inguinal node metastases, or large (2-4 cm) inguinal nodes, or if the most proximal femoral (Cloquet's) node is involved, although there is no evidence that this provides any survival benefit (GR C).

19. Performing ILND before proceeding to PLND has the advantage that PLND can be avoided in patients with minimal inguinal node involvement, thus reducing the greater risk of complications (especially chronic lymphedema) resulting from combined ILND and PLND (GR B).
20. In patients with palpable inguinal nodes, performing PLND with frozen section prior to ILND has the advantage that, if the pelvic nodes are positive, ILND can be avoided (since it is not curative) and the patient treated with chemotherapy; the disadvantage is that, if the pelvic nodes are negative, ILND still has to be performed, thus increasing the risk of lymphoedema (GR C).
21. In patients with numerous or large histologically proven inguinal metastases, CT or MR can be performed, and if there are grossly enlarged iliac nodes, neoadjuvant chemotherapy should be given and the response assessed before proceeding with PLND (GR C).
22. SNB or modified (limited) ILND can be used to reduce the risk of postoperative surgical complications, but it may increase the risk of incomplete removal of node metastases, thus possibly compromising survival (GR C).
23. Antibiotic treatment should be started prior to surgery to minimize the risk of wound infection, but the optimal duration of antibiotic administration is undefined (GR C).
24. Heparin for the prevention of thrombo-embolic complications may be used, although heparin may increase lymph leakage (GR C).
25. The skin incision for ILND should be parallel to the inguinal ligament, following the natural skin lines, and sufficient subcutaneous tissue should be preserved to minimize the risk of skin flap necrosis (GR B).
26. Sartorius muscle transposition to cover the exposed femoral vessels can be used after radical (complete) ILND, although there is no clear evidence that it reduces the risk of postoperative complications (GR C).
27. Closed suction drainage is useful after ILND to prevent fluid accumulation and wound breakdown, although there is no clear evidence that it reduces postoperative complications (GR B).
28. Fibrin sealant (glue) may be used after ILND to prevent lymph leakage, although there is no clear evidence of benefit (GR C).
29. Early postoperative mobilization is recommended, unless immobilization is advisable to preserve the blood supply to myocutaneous flaps (GR B).
30. Elastic stockings or sequential compression devices are advisable to minimize the risk of lymphedema and thrombo-embolism, but there are no data from studies in penile cancer patients after ILND to prove its benefit (GR C).
31. Radiotherapy (RT) to the inguinal areas in patients without cyto- or histologically proven lymph node metastases (i.e. prophylactic RT) is not recommended, because it is not guaranteed to eradicate occult metastases, it may make surveillance more difficult, and may increase the morbidity and decrease the cure rate of surgery if there is inguinal recurrence (GR B).
32. RT to the inguinal areas in patients with microscopic lymph node metastases proven on FNAC or SNB (i.e. therapeutic RT) is not recommended, for the same reasons as above, but it may be considered for bulky node metastases as neo-adjuvant to surgery (GR B).
33. Adjuvant RT after complete ILND can be considered in patients with multiple or large inguinal node metastases or extranodal extension of malignancy, but it can render clinical follow-up more difficult (GR C).
34. Adjuvant chemotherapy after complete ILND can be used instead of RT in patients with inguinal node metastases that are multiple (more than 2), large or with extranodal extension, or if there is pelvic node metastasis (GR C).
35. Follow-up should be individualized, with the intervals and duration of visits determined by the histopathological features and initial management chosen for the primary tumor and inguinal nodes (GR B).

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Committee 7

Treatment of Visceral or Bulky/unresectable Regional Metastases of Penile Cancer

Chair

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Lance Pagliaro (USA)

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Treatment of Visceral or Bulky/unresectable Regional Metastases of Penile Cancer

Treatment of Visceral or Bulky/unresectable Regional Metastases of Penile Cancer

C. A. Pettaway

L. C. Pagliaro, C. Theodore, G. P. Haas

Background

The presence and extent of metastases dictate survival in squamous cell penile cancer. The inguinal region is virtually always the initial site of metastatic disease prior to further distant dissemination. Based on the results of prior retrospective studies, ilioinguinal lymphadenectomy alone can be curative among patients with limited unilateral inguinal metastases, where no extranodal extension exists and the pelvic lymph nodes are uninvolved.[1-4] Among patients thought to have surgically curable disease, if adverse pathologic factors are discovered, adjuvant therapeutic strategies could then be considered in order to improve survival.[5-6]

The purpose of this chapter is to review our current state of knowledge in the management of patients presenting with stage IV penile cancer, characterized as bulky or unresectable regional disease or visceral metastases, occurring either as an initial presentation or disease recurrence. The goal is to define the roles of surgery, radiation, and systemic therapeutic strategies in providing cure or palliation from an evidence-based approach.

For the purposes of this study articles related to the topics *advanced penile cancer, metastatic penile cancer* alone and combined with *chemotherapy, radiation therapy* and *inguinal lymphadenectomy* were reviewed. Articles were shared with the panel and rated as to their level of evidence based upon the criteria of the Oxford Center for Evidence-Based Medicine. Subsequent to this review recommendations were made by consensus for the management of stage IV penile cancer, with the appropriate grades based upon the level of evidence.

Incidence

The Stage IV definition for this chapter includes: (1) clinical N3, or M1 disease based upon the sixth edition TNM system (that reflects deep inguinal or pelvic nodes, and distant metastasis respectively i.e., TNM stage IV);[7] (2) the presence of a fixed nodal inguinal mass (i.e., clinical extranodal extension of cancer) included in a modified TNM staging system (i.e, N3) as proposed by Leijte et al.[8] and (3) Jackson stage IV penile cancers, used to denote inoperable inguinal or distant metastasis in older penile cancer case series.[9]

Table 1 provides data from large retrospective and prospective penile cancer case series from 1952 to 2006.[4,8,10-16] Overall the incidence of stage IV disease by the current or modified TNM or Jackson descriptions ranged from 0-14%. Among series stratifying bulky or unresectable lymph nodes the incidence was 0-13.4% with the highest incidence noted in a series from India.[14] Among two contemporary prospective case series where the incidence of distant metastases was categorized separately from inguinal/pelvic disease the incidence ranged from 1.9%-7% at initial presentation or disease recurrence.[8,16] Bulky inguinal or pelvic metastases were the most common presentation of stage IV disease with the most common distant sites being (1) distant nodal, (2) lung, and (3) bone, as well as (4) other soft tissue sites. Liver and brain sites of metastasis have also been reported in other series (Fig. 1).[3,10,17-19]

Table 1: Stage IV penile cancer: incidence 1952-2006						
Author	**# of patients**	**Years**	**N3**	**M1/Jackson IV**	**Survival**	**Evidence level**
Merrin[10]	129	1952-79	-	18 (14%)	3.5%, 2 mos.	retrospective case series-3
Narayana et al.[11]	219	1936-75	-	0	-	retrospective case series-3
Fraley et al.[12]	94	1952-75	-	11 (11.7%)	-	retrospective case series-3
Persky and deKernion[13]	77	1954-74	-	6 (7.8%)	<12 mos.	retrospective case series-3
Pandey et al.[14]	425	1987-97	57 (13.4%)	-	-	retrospective case series-3
Ornellas et al.[4]	414	1960-87	40 (9.6%)	-	40%, 2 mos.	retrospective case series-3
					20%, 6 mos.	
					10%, 12 mos.	
Leijte et al.[8]	513	1956-06	31 (6%)	10 (1.9%)	N3 median = 12 mos.	prospective case series-3
					M1=0 , 12 mos.	
Ritchie et al.[15]	193	1997-99		9 (4.6%)	7/9 (78%) dead, 12 mos.	prospective case series-3
Hegarty et al.[16]	100	2002-05		7 (7%)	5/7 (71%) dead	prospective case series-3
					Median 3 mos. (1-17)	

Natural history, presentation, diagnostic evaluation

Enlarging inguinal metastases are usually the initial presenting feature that can take a relentless progressive course leading to skin necrosis, chronic infection and death from: 1) sepsis, 2) hemorrhage secondary to erosion into the femoral vessels or 3) progressive "failure to thrive" from tumor associated cachexia. Weight loss, fatigue, pain, and malaise are common presenting signs of advanced loco-regional disease. As these symptoms and findings usually take precedence, it is rare that symptoms referable to the distant metastatic site are noted clinically at the outset.[3]

The diagnosis of stage IV disease may be evident, based upon physical examination. However, cross sectional imaging with computed tomography (CT), magnetic resonance (MR) along with chest radiography is indicated in patients presenting with palpable inguinal adenopathy to define the extent of disease. A bone scan is useful, with plain films among patients who have symptoms referable to bone metastases.[3]

Laboratory studies may be completely normal, but anemia, leucocytosis, and hypoalbuminemia may be present in patients with longstanding progressive disease associated with blood loss, infection and malnutrition. Azotemia may develop secondary to nodal obstruction of the ureters. Of importance among patients with stage IV penile cancer, a serum calcium should be obtained as hypercalcemia occurred in 17%-21% of patients in two series.[17,20] This is thought to be related to parathyroid hormone and related substances produced by bulky metastases that stimulate osteo-

clastic bone resorption.[3,21] Thus gross bone involvement is not required for hypercalcemia to occur. Management is aimed at forcing a saline diuresis with volume expansion as well as inhibition of osteoclast function with bisphosphonate therapy.[3]

Irrespective of the site involved, most patients with stage IV disease based upon the available data succumb to their disease within one year (Table 1).

We review treatment strategies to provide insight into potentially curative or palliative therapy that can guide current management, with recommendations based upon available evidence.

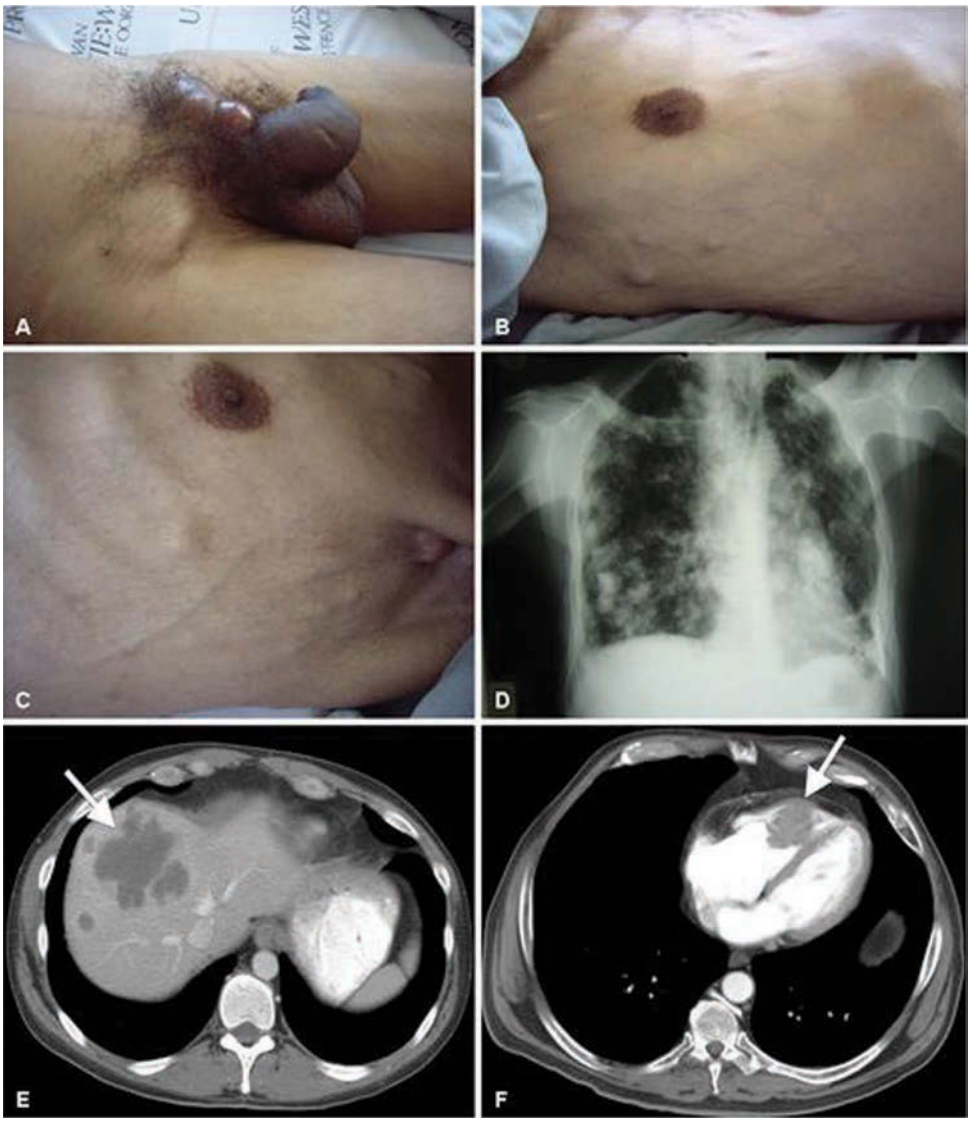

Fig. 1: *Metastatic dissemination of penile cancer.*
(A) bulky inguinal metastases
(B-C) distant cutaneous metastases
(D) lung metastases
(E) liver metastases
(F) intracardiac metastases.
Figs. A-C from Van der Merwe et al.[22]

Chemotherapy for stage IV penile cancer

There are several published phase II clinical trials of combination chemotherapy, providing evidence for the treatment of metastatic penile cancer (LE 3). Being a rare disease, these trials are small and no study has ever been replicated as a confirmatory measure. There are also no randomized trials, and comparison of treatment results from different trials is complicated by differences in patient characteristics such as prior therapy and stage of disease. We reviewed the data from 5 different combination regimens reported since 1990 and, for comparison, two earlier studies of single-agent chemotherapy.

▪ Single-agent chemotherapy

The SWOG study of single-agent cisplatin[23] (50 mg/m^2 IV on days 1 and 8 of each 28-day cycle) was the largest phase II chemotherapy (CT) trial up to that time, with 26 patients evaluable for response (Table 2).[24-29] All but one patient were stage IV and none had received prior CT. The median age was 56 (range 35-85) years. There were 4 partial responses (PRs) in patients with tumor limited to skin and lymph nodes, for an overall response rate (ORR) of 15% (95% CI 4.4%-34.9%). Response duration was 1-3 months and the median overall survival was 4.7 months (Table 3).

A smaller study by Ahmed et al.[24] treated patients with single-agent cisplatin, methotrexate, or bleomycin. Drugs were continued until progression and were given sequentially to look for evidence of cross-resistance. Twelve patients were evaluable for response to cisplatin, of whom 9 had received prior CT. Cisplatin was given once every 3 weeks, at varying doses (70-120 mg/m^2). Median age was 54 (range 40-69) years. One patient had complete response (CR) lasting 7 months, and 2 had PRs lasting 2 and 8 months, for an ORR of 25%. This was within the 95% confidence interval reported in the SWOG study.

Fourteen patients were evaluable for response to single-agent bleomycin (with variation in dose, schedule, and infusion time). There was one CR, but the patient died from pulmonary toxicity of the drug. There were also two PRs, for an ORR of 21%. One of the responders had received prior CT. The median response duration was 3 (range 2-4) months.

Thirteen patients received single-agent methotrexate, of whom 5 patients had received prior cisplatin or bleomycin. There were 8 responders (61.5%), of whom 3 had received prior cisplatin; one was a CR. The median response duration was 3 (range 2-31) months. One patient died from treatment-related sepsis. The Ahmed et al. study results did not suggest cross-resistance to bleomycin, methotrexate, or cisplatin, which stimulated interest the in the 3-drug combination (BMP).

▪ Combination chemotherapy

A SWOG phase II study of BMP[25] included 40 evaluable patients with median age of 57 (range 23-81) years. The response rate was 32.5% (5 CR, 8 PR), again being within the 95% CI range for single-agent cisplatin. There were 5 treatment-related deaths, one from infection and 4 from pulmonary complications. The median duration of response was 16 weeks, and median overall survival was 28 weeks.

Table 2: Treatment series with LE 3

Author (year)	No. patients (evaluable)	Drug or regimen	Prospective study
Ahmed et al. (1984)[24]	13 (13)	Methotrexate	No
	14 (12)	Cisplatin	No
	14 (14)	Bleomycin	No
Gagliano et al. (1989)[23]	26 (26)	Cisplatin	Yes
Shammas et al. (1992)[26]	8 (8)	Fluorouracil, cisplatin	No
Haas et al. (1999)[25]	45 (40)	BMP	Yes
Skeel et al. (2003)[27]	18 (16)	Interferon-alpha, 13-CRA	Yes
Pagliaro et al. (2006)[28]	20 (20)	TIP	Yes
Theodore et al. (2008)[29]	28 (26)	Irinotecan, cisplatin	Yes

Abbreviations: BMP, bleomycin, methotrexate, cisplatin;
13-CRA, 13-cis-retinoic acid;
TIP, paclitaxel, ifosfamide, cisplatin

Table 3: Safety and efficacy of bleomycin, methotrexate, and cisplatin			
Drug or regimen	**ORR**	**Treatment-related deaths**	**Median overall survival**
Bleomycin[24]	21%	1/14	Not reported
Methotrexate[24]	1.5%	1/8	Not reported
Cisplatin[24]	25%	Not reported	Not reported
Cisplatin[23]	15%	0/26	4.7 months
BMP[25]	32.5%	5/40	28 weeks

Abbreviations: ORR, overall response rate; BMP, bleomycin, methotrexate, cisplatin.

There is sufficient evidence to evaluate the safety and efficacy of 4 additional multidrug regimens (Table 4) (LE 3). A regimen would be of interest if it achieves an ORR significantly greater than 30% without producing life-threatening toxicity. The combination of paclitaxel, ifosfamide, and cisplatin (TIP) had an ORR of 55% in a preliminary (abstract) report.[28] The final results of this study have not yet been published, but results from the first 20 patients suggest that TIP is at least as effective as BMP and has less toxicity. Both TIP and irinotecan/cisplatin[29] have been used in the neoadjuvant setting with reported cases of negative pathology in resected lymph nodes (Table 5), and some responding patients have enjoyed long-term disease-free survival.

Table 4: Safety and efficacy of multidrug regimens without bleomycin			
Regimen	**ORR**	**Treatment-related deaths**	**Median overall survival, months**
Fluorouracil, cisplatin[26]	25%	0/8	11.5
Interferon-alpha, 13-CRA[27]	6%	0/17	4
TIP[28]	55%	0/20	11
Irinotecan, cisplatin[29]	30.8%	0/28	4.7

Abbreviations: ORR, overall response rate; 13-CRA, 13-cis-retinoic acid; TIP, paclitaxel, ifosfamide, cisplatin.

Table 5: Results of post-chemotherapy lymphadenectomy		
Chemotherapy	**Lymphadenectomies performed**	**Negative pathology in lymph nodes**
Fluorouracil, 1000 mg/m^2/day days 1-5 CI Cisplatin, 100 mg/m^2, day 1 Cycle every 3-4 weeks[4]	1	0
Paclitaxel, 175 mg/m^2, day 1 Ifosfamide, 1200 mg/m^2, days 1-3 Cisplatin, 25 mg/m^2, days 1-3 Cycle every 3 weeks[6]	17	2
Irinotecan, 60 mg/m^2, days 1, 8, 15 Cisplatin, 80 mg/m^2, day 1 Cycle every 4 weeks[7]	3	3

Abbreviation: CI, continuous infusion.

The use of bleomycin in the treatment of men with penile cancer was associated with an unacceptable level of toxicity (Table 3). Single-agent methotrexate had a 61.5% response rate in a small series, but was also associated with life-threatening toxicity, and the high response rate was never confirmed or supported by the results of combination regimens, such as BMP, that contained methotrexate (Table 3). The median survival with these treatments in patients with advanced metastatic penile cancer was only 4-5 months.

Other cisplatin-based combinations show response rates of 25%-55% (Table 4). Median survival of 11 months, reported in two of the studies, appears to be an improvement over BMP or single-agent CT, but could also reflect the inclusion of earlier stage patients. The TIP study,[28] in particular, was a neoadjuvant study from which patients with visceral metastases or lymph node involvement above the aortic bifurcation were excluded. The earlier stage of disease at study entry may account for a longer median survival. The fluorouracil/cisplatin study[26] was retrospective and very small, with only 8 patients, making it difficult to reach any firm conclusions about efficacy. The irinotecan/cisplatin study[29] conducted by the EORTC was prospective, and larger, with 26 evaluable patients, but was interpreted as a negative result by the authors because the response rate had an 80% confidence interval (18.8%- 45.1%) extending well below 30%.

Selected patients with advanced, unresectable primary tumors or bulky regional lymph node metastases appeared to benefit from post-chemotherapy lymphadenectomy (Table 5). Negative pathology in lymph nodes was seen after neoadjuvant treatment with TIP (2/20 patients) and irinotecan/cisplatin (3/7 patients).

For patients with unresectable primary tumors or bulky regional lymph node metastases, neoadjuvant treatment with a cisplatin-containing regimen may be effective and may allow curative resection. The optimal CT regimen has yet to be determined. The final results of the TIP neoadjuvant study, when reported, should be compared with the disease-free and overall survival expected with lymphadenectomy alone in similar-stage patients.

The published data do not support the use of bleomycin or BMP for palliative treatment of advanced metastatic disease. The data suggest, though not conclusively, that the cisplatin-based regimens shown in Table 4 have a higher ORR and longer median survival than single-agent cisplatin.

Radiotherapy for stage IV penile cancer

Successful management of bulky or unresectable lymph node metastases from squamous cell carcinoma of the penis involves combination therapies of surgery, CT and/or radiation therapy (RT). There are no high level evidence publications in the literature supporting individual approaches, but there are several smaller series providing informative data, and experience with chemo-radiation therapy of squamous cell cancers from other sites (vulvar and anal canal) that support combination therapy for unresectable penile cancer.

One of the largest series demonstrating a benefit of RT for lymph node metastases and/or distant metastases from penile cancer was published by Ravi and associates in 1994[30] and constitutes LE 3. One hundred and twenty patients with lymph node metastases and 9 with distant metastases were managed by RT alone (palliative) or in the preoperative or postoperative setting. Pertinent to the advanced disease presentation setting 33 patients were treated with preoperative RT at 40 Gray (Gy) over 4 weeks and subsequently had inguinal lymphadenectomy. Of note, after RT and surgery only 8% had evidence of extranodal extension (ENE) and 3% recurred within the groin. This is relevant as in a prior report within a contemporary time frame the incidence of ENE was 33% among patients treated with surgery alone and groin recurrence was noted in 19%. The difference for both ENE and local recurrence were both statistically lower ($p=<0.01$ and 0.03, respectively). The data are strongly suggestive but not definitive that preoperative RT for nodes ≥4cm without skin fixation improved local control. The 5-year survival among the latter group was 70% (Table 4). Palliative RT ameliorated symptoms in 56% of patients with fixed groin nodes,

in 5/5 patients with painful bony metastases, and in 1/2 patients with spinal cord compression and paraplegia. However, pelvic and/or para-aortic RT was ineffective in patients with pelvic node metastases (Table 6).

Table 6: Radiation therapy for lymph node and distant metastases - adapted from Ravi et al.[30]

Time of Treatment	Indication	No. of groins	No. of patients	CR	PR	<PR	Palliation of symptoms	Subsequent groin dissections	5-Year (%) DFS
Preoperative: Inguinal RT	Nodes >4cm in size not fixed to underlying structures or overlying skin	38	33	1	6	31	-	38	23 (70)
	Nodes of any size fixed to overlying skin but mobile	14	12	-	2	12	-	7	2 (17)
Post-operative: Inguinal RT	Perinodal infiltration in the inguinal region	14	12	-	-	-	-	-	1 (8)
Pelvic RT	Metastatic pelvic nodes on lymphadenectomy	20	18	-	-	-	-	-	0
Pelvic RT Pelvic & para-aortic RT	Metastatic pelvic nodes on lymphadenectomy	4	4	-	-	-	-	-	0
Palliative: Inguinal RT	Nodes fixed to underlying structures with or without skin infiltration/fungation	66	41	1	2	63	23	2	1 (2)
Local RT to bone	Painful bony metastasis	-	5	-	-	-	5	-	0
Spinal RT	Cord compression and paraplegia	-	2	-	-	-	1	-	0
Supraclavicular RT	Supraclavicular nodal metastasis	-	2	-	-	-	-	-	0

Abbreviation: DFS, disease-free survival.

▪ Lessons from other squamous cell malignancies

In women with cancer of the vulva, a disease site that has a natural history and nodal drainage similar to that of the penis, Hyde et al.[31] reported that debulking plus adjuvant radiotherapy (RT) was as effective as full groin dissection. Parthasarthy et al.[32] noted that after primary node dissection, there was improved disease-free survival when they received adjuvant postoperative RT.

Specific to bulky inguinal nodes at presentation the Gynecologic Oncology Study Group performed a phase two study to assess the efficacy of preoperative chemoradiation prior to inguinal lymphadenectomy among patients with bulky N2/N3 inguinal nodes from vulvar squamous cancer.[33] Forty two patients received split course chemoradiation consisting of cisplatin (50mg/m^2) and 5-fluorouracil [5-FU] (1000mg/m^2) combined with 4760 cGy RT to the primary tumor and inguinal nodes. In total 37 of 38 patients taken to surgery had an inguinal dissection and in 15 (40.5%) no tumor was found. Thirty-six of 37 patients (97%) had no inguinal recurrence. However, only twelve patients (31%) remained alive without evidence of disease at 78 months follow-up as death due to other causes (7) and distant metastases (9)

occurred. Thus preoperative chemoradiation in this prospective study improved resectability and local control among this cohort of patients with bulky inguinal metastases.[33]

Among patients with anal squamous cell cancer the addition of CT (5-FU and mitomycin) to RT decreased the local recurrence rate by 46% and improved disease specific survival in a randomized prospective trial.[34] Green et al.[35] performed a systematic review of the literature and meta-analysis to assess the efficacy of concomitant CT and RT in the treatment of squamous cancer of the cervix. The analysis included 4,580 patients with 62%-78% available for analysis. Concomitant CT proved to be superior to RT alone in both overall response rate (HR=0.71 p<0.0001) and progression free survival (0.61 p<0.0001) and reduced local and distant recurrence. However, this occurred at the cost of significantly greater toxicity in the combination arm.

In summary, for advanced stage penile cancer there is evidence that preoperative RT for bulky non-fixed nodes may improve resectability and decrease local recurrence. In the palliative setting use of RT may decrease pain from fixed inguinal masses as well as bone metastases.[30] Based on the available data from other squamous malignancies the use of chemoradiation should be further explored in multi-institutional trials.

Surgical consolidation in stage IV penile cancer

Penile cancer exhibits a prolonged regional phase prior to distant dissemination and therefore ilio-inguinal lymphadenectomy can be curative in patients with inguinal metastases. However, a "therapeutic window" exists related to the volume of inguinal metastases when surgery is performed that predicts for cure. Available data suggest that such patients have unilateral limited metastases without extranodal extension of cancer or pelvic metastases.[1-4] Thus, does surgery have any role in the management of stage IV penile cancer, alone or as part of a multi-modal strategy?

Ornellas et al.[4] described an extensive lymphadenectomy series in 1994 that included 414 patients of whom 40 exhibited clinical N3 nodal metastases. Twenty four patients underwent a palliative dissection, of whom only 5 (21%), 2 (8%), and 1 (4%) survived 1, 2, or 3 years, respectively (Fig. 2). They noted improved "short term" quality of life and no perioperative deaths. The actual cause of death and whether patients experienced wound recurrences was not mentioned. One would also presume that the 24 of 40 patients selected for surgery represented the most fit of the group. Thus, while surgery can often accomplish removal of an infected, sometimes painful primary, cure is not achieved and the duration and quality of palliation in stage IV penile cancer with surgery alone is questionable.

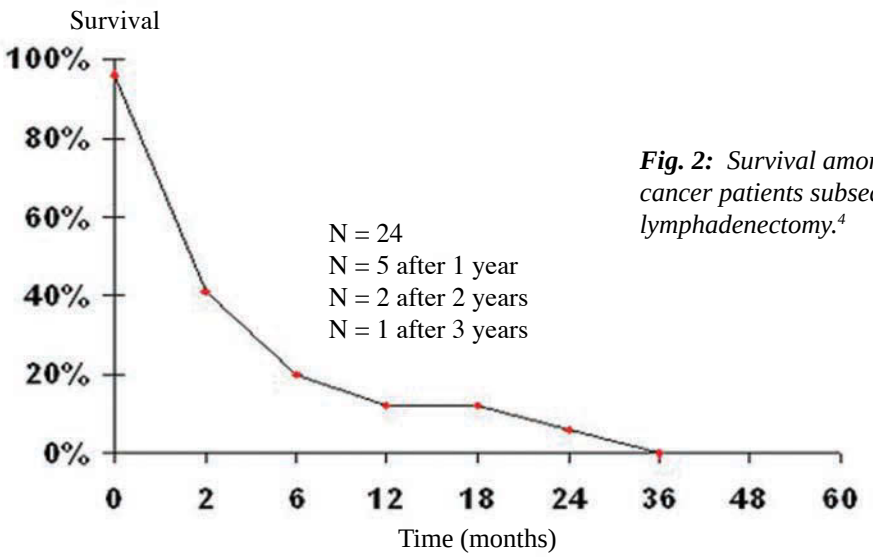

Fig. 2: *Survival among 24 stage IV penile cancer patients subsequent to palliative inguinal lymphadenectomy.*[4]

Considering that surgery as monotherapy for this disease stage is inadequate in sterilizing the regional field and does not address distant metastases, several series have described multimodal approaches utilizing systemic CT and surgery in patients with bulky inguinal metastases (Table 7). The available data are limited in most cases to retrospective reviews of patients with either initial or recurrent bulky metastases treated with systemic CT and then subsequently undergoing a surgical procedure. The peer reviewed literature describes approximately 63 patients to date (Table 7).

▪ Individual series

Shammas et al. in 1992 reported on 8 patients treated with the combination of cisplatin and 5-fluorouracil.[26] Seven of the eight patients had Jackson stage III or IV disease and two in this group had either pleural or lung metastases. One of 7 (14%) had a PR with disappearance of lung metastases and post-surgical consolidation and lived 32+ months. He received 5 cycles of therapy. Three patients with stable disease received only 1-2 cycles and survived 2+ to 11 months. Of note two of three patients who ultimately had disease progression received 3-4 cycles of therapy and underwent surgical consolidation with survivals of 12 and 28 months from CT.

Thus, 2 of 7 patients (28%) who survived 28 and 32+ months received significant palliation or cure from the combination. Corral et al.[18] reported on the long-term follow-up of a prospective group of patients treated with bleomycin, methotrexate and cisplatin. Among the cohort, 21 patients had penile carcinoma with 10/21 (48%) having either N3 or M1 disease. The remainder had either N1 or N2 nodal metastases. Objective responses were noted in 12 (57%) including 2/5 with distant metastases. Six patients in the group (28.5%) achieved disease-free status with either CT alone (2) or surgery (3) or RT (1) with a median survival of 27.8 months. This was significantly longer than that of those not achieving disease-free status (6.7 months, p=0.004). Thus, this prospective study showed that a multidisciplinary approach to achieve disease-free status could prolong survival (LE 3).

Subsequently Leijte et al.[36] from the Netherlands Cancer Institute reviewed their experience with neoadjuvant CT in patients with initially "unresectable" penile cancer. The series included 20 patients treated with 5 different regimens including 1) single agent bleomycin, 2) bleomycin, vincristine, methotrexate; 3) cisplatin, 5-fluorouracil; 4) bleomycin, cisplatin, methotrexate; and 5) cisplatin, irinotecan. The objective responses were evaluable in 19 (one patient died due to bleomycin toxicity after two weeks) with 12 responses (63%, 2 complete, 10 partial). Surgical procedures included treatment of the primary tumor as well as inguinal and pelvic dissections. Additional soft tissue resection including bone was sometimes required. Vascularized tissue flaps were used for inguinal reconstruction.[36] Among 12 responders only 9 went to surgery, as two died of bleomycin related complications while the third was deemed unfit for surgery. Eight of nine responding patients taken to surgery (two were pT0) were free of disease with a median follow-up of 20.4 months. This is in contrast to three nonresponders who went to surgery for palliative intent. All three died within 4-8 months due to loco-regional recurrence (Fig. 3). The implications from this study indicate that response to CT together with an aggressive surgical procedure provides the optimal scenario for significant palliation or potential cure (LE 3). However, the authors questioned the role of bleomycin containing regimens because of their toxicity.

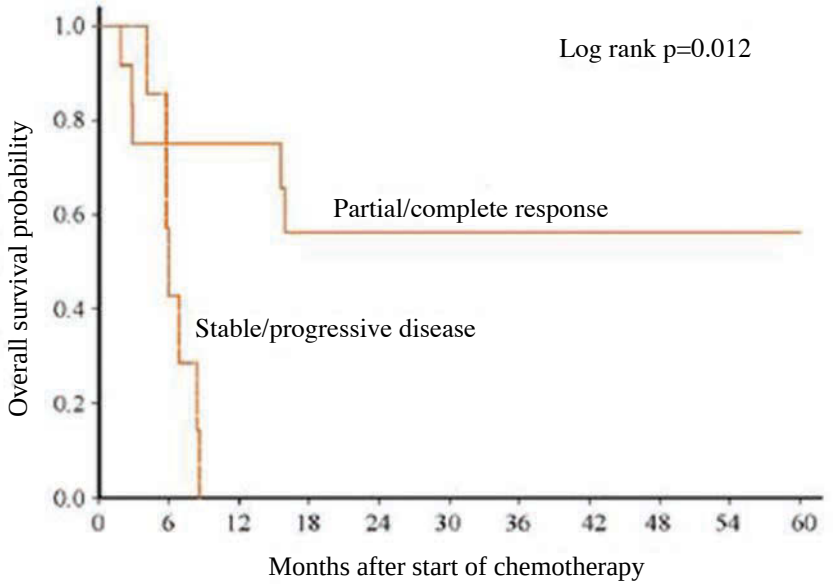

Fig. 3: *Comparative survival based upon response among patients treated with neoadjuvant chemotherapy and surgery.*[36]

In a separate study Bermejo et al.[19] described the surgical considerations and complications among 10 patients who had either a response or stable disease after combination CT. The regimens utilized included 1) bleomycin, methotrexate, cisplatin; 2) paclitaxel, ifosfamide, cisplatin (TIP), or paclitaxel, carboplatin. This cohort of patients exhibited bulky inguinal or pelvic metastases with the only exclusions being patients with fixed pelvic masses or complete encasement of the femoral vessels. In addition to ilioinguinal lymphadenectomy, resection of the inguinal ligament, the inferior aspect of the rectus abdominis or external and internal oblique muscles, the spermatic cord and ipsilateral testicle, and segments of the femoral artery and vein (with subsequent patch or bypass grafting) were performed in order to achieve negative margins. Plastic surgery consultation was obtained for wound coverage, including the insertion of monofilament polypropylene mesh for abdominal wall defects and myocutaneous flaps of the sartorius, rectus abdominus, serratus anterior, and latissimus dorsi muscles.[19] Among 5 patients exhibiting an objective response three were alive and disease-free at 48, 50, and 73 months. Two other patients died (one of disease at 30 months, another of unknown causes at 21 months). Among the 5 remaining patients with stable disease 3 were dead of disease within 7 months, 1 patient treated with bleomycin died of "failure to thrive" at 8 months. However, another patient treated with paclitaxel and carboplatin achieving only stable disease was alive and disease-free at 84 months. These data appear to reinforce the concept that response to systemic CT prior to surgery enhances the chance for long-term survival among those undergoing surgical resection. Related to systemic therapy the authors reported that the TIP regimen was well tolerated and all three pT0 responses at surgery were among patients treated with TIP. This provided the rationale for the prospective phase II study discussed previously.[28]

Providing additional rationale to consider a taxane based regimen in patients with advanced penile cancer as part of a multi-modal strategy, Pizzocaro et al.[37] recently reported on six patients (5/6 with N3 metastatic nodes) who were treated with paclitaxel (one patient received docetaxel), cisplatin and 5-fluorouracil. Post-surgery, three patients exhibited a pathologic CR. Two of the three received 5-7 cycles of therapy and were NED at 25-27 months. The third patient tolerated only two cycles of therapy and although he was pT0 at surgery he relapsed at 11 months and died. Another patient with pathologic PR (>90% necrosis in specimen) also received only 2 cycles of therapy but was NED at 46 months. A patient with a clinical CR refused surgical consolidation and relapsed and died at 6 months, as did the only remaining patient with no response to therapy (4 months survival). Taken together these data pro-

vide evidence that response to CT improves resectability and survival. Surgery among patients who do not respond to therapy may occasionally be associated with long-term survival, but is more often associated with death due to either rapidly occurring locoregional recurrence or distant metastases.[19,36]

Table 7: Postchemotherapy surgical consolidation in penile cancer

Series	Year	# of patients	Preoperative chemotherapy	Response	Consolidative surgery	Survival	Evidence level
Shammas et al.[26]	1992	7	cisplatin 5-fluorouracil	PR=1 Stable=3 Prog.=3	1 2 2	32+ mos. 8, 11 mos. 12, 28 mos.	retrospective case series-3
Corral et al.[18]	1998	21	BMP[3]	R=12 Other=9	4[1]	27.8 mos.[2]	prospective case series-3
Leijte et al.[36]	2007	19	BMP[3]/others[4]	R=12 Prog.=7	9 3	8/9 alive 20.4 mos. 0/3 alive 12 mos.	retrospective case series-3
Bermejo et al.[19]	2007	10	BMP[3] TIP[5] PC[6]	CR=4 PR=1 Stable=5	4 1 5	2/4 alive, 48 mos. 1/4 dead unknown 21 mos. 1/4 dead of disease alive 50 mos. 3/5 dead of disease, 7 mos. 1/5 dead other, 8 mos. 1/5 alive, 84 mos.	retrospective case series-3
Pizzocaro et al.[37]	2008	6	P (doc) cisplat, 5-FU[7]	CR=4 PR=1 Prog=1	3 1 1[1]	2/3 alive, 25, 27 mos. 1/3 dead of disease, 11 mos. 1 clinical CR, dead of disease, 6 mos. alive 46 mos. dead of disease, 4 mos.	prospective case series-3

1. One patient received radiotherapy
2. Median survival among six patients who became disease-free via chemotherapy=2, surgery=3, or radiotherapy=1
3. Bleomycin, cisplatin, methotrexate
4. Single agent bleomycin, bleomycin, vincristine, methotrexate; cisplatin, 5 fluorouracil, cisplatin, irinotecan
5. Paclitaxel, ifosfamide, cisplatin
6. Paclitaxel, carboplatin
7. Paclitaxel or docetaxel, cisplatin, 5 fluorouracil

- **Complications**

The feasibility of performing aggressive surgical resection and reconstruction in the post-CT setting was briefly described by Bermejo et al. and Leijte et al.[19,36] in that there were no perioperative deaths. Bermejo et al. noted three major perioperative complications, including a thigh hematoma requiring inguinal re-exploration to drain the hematoma, acute renal failure, and deep venous thrombosis.[19] Minor complications included skin breakdown in three cases and wound seroma in one. In an earlier series from M.D. Anderson Cancer Center Bevan-Thomas et al.[38] compared the complication rates in patients undergoing either prophylactic, therapeutic, or palliative dissections. The latter included patients treated with preoperative CT. The incidence of complications was greater among those undergoing a palliative dissection (8/12 = 67%) versus either prophylactic (23/66 = 35%) or therapeutic (10/28 = 36%) dissections (p=0.01, 0.04, respectively). A single postoperative death was reported in this series in a patient with a fungating mass. Despite preoperative wound care and antibiotics he succumbed to sepsis in the postoperative period. Thus taken together the available literature suggests that the optimal candidates for postchemotherapy surgical consolidation in advanced penile cancer are those with a significant response to therapy who are fit and whose inguinal disease is grossly free of infection.

Palliation in stage IV penile cancer

Palliative care among patients with advanced regional disease can be difficult to achieve. The goals would be to alleviate pain, maximize wound care, treat associated hypercalcemia, and prevent impending femoral vessel rupture. Prior to combination CT regimens for penile cancer, Block et al. described 7 patients with recurrent inguinal masses that had grown despite prior surgery or RT and who were treated with hemipelvectomy.[39] Six of 7 patients were less than 50 years of age. All seven patients underwent a hemipelvectomy and three were alive and disease-free at 4, 7, and 10 years. The other four died within one year. The main factor associated with success appeared to be unilateral involvement with no disease crossing the midline.[39] In the current era of combination CT this procedure could have a role among selected young patients with extensive unilateral involvement of the femoral vessels or the ipsilateral pubis who respond to therapy but in whom achieving a tumor-free negative margin could not be achieved by less radical means. As noted in the prior section, RT was beneficial in improving pain from fixed inguinal masses, bony involvement, and cord compression.[30] Emergent intervention with endoluminal vascular stents can at least temporarily alleviate vascular hemorrhage from tumor erosion into the femoral vessels.[40] Treatment of hypercalcemia is readily accomplished with intravenous saline for volume expansion to promote diuresis and with bisphosphonates to prevent osteoclastic bone resorption.[3] Lastly, hospice referral is valuable to both patient and family for pain control and coordination of end-of-life issues.

Recommendations for the management of stage IV penile cancer

Diagnosis should be based on tumor biopsy, physical examination, and imaging studies to define the histology and extent of disease. Appropriate laboratory studies are performed and should include those important to guide patient management, including complete blood count, liver function tests, creatinine level, calcium, alkaline phosphatase, and albumin.

1. Treatment with a cisplatin-containing regimen in stage IV penile cancer should be considered, as responses do occur and this may facilitate curative resection. The optimal chemotherapy regimen has yet to be determined (LE 3, GR B).
2. The use of bleomycin in the treatment of men with penile cancer was associated with an unacceptable level of toxicity and is discouraged as first line therapy (LE 3, GR B).

3. Surgical consolidation to achieve disease-free status or palliation should be considered in fit patients with a proven objective response to systemic chemotherapy (LE 3, GR B).
4. Surgical consolidation among patients who progress through chemotherapy is not recommended (LE 3, GR B).
5. Preoperative inguinal radiotherapy among patients with nodes ≥4 cm without skin fixation may improve surgical resectability and decrease local recurrence. The morbidity of this combined strategy requires further study (LE 3, GR C).
6. Inguinal radiotherapy may be of palliative benefit postchemotherapy among patients with unresectable inguinal, or bone metastases (LE 3, GR C).

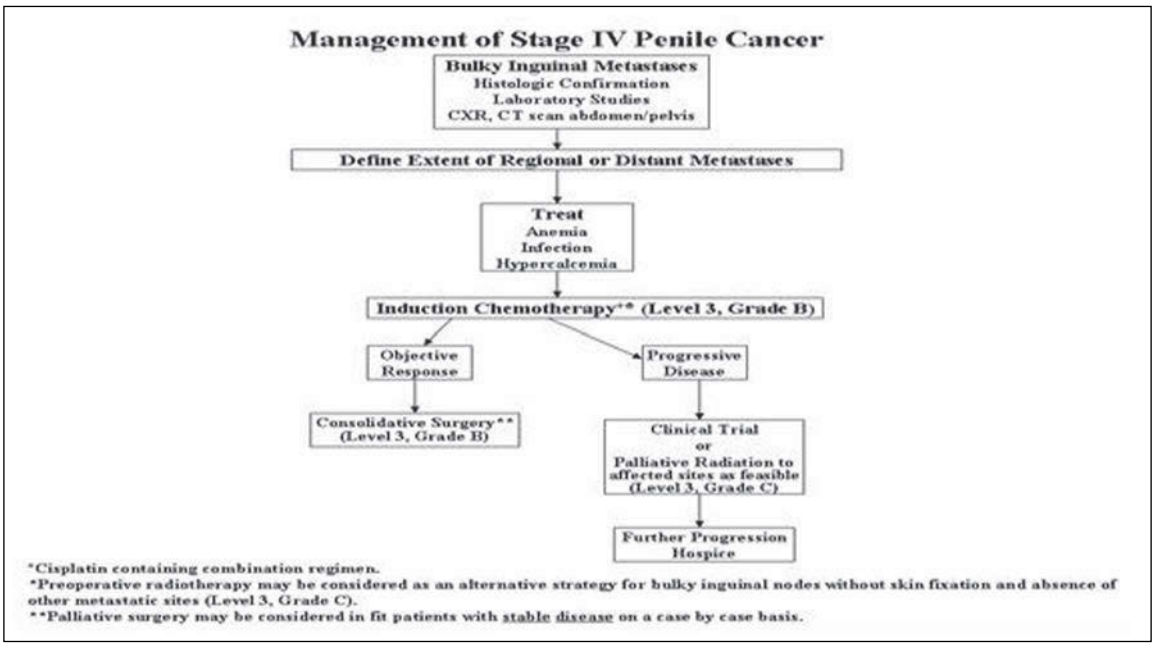

Fig. 4: *Treatment algorithm for stage IV penile cancer.*

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Committee 8

Prognostic Factors in Penile Cancer

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CONTENTS

Prognostic Factors in Penile Cancer

V. Ficarra

B. Akduman, O. Bouchot, J. Palou, M. Tobias-Machado

Squamous cell carcinoma (SCC) of the penis arises in about 95% of cases from the distal portion of the penis, involving the prepuce and/or the glans and/or the distal extremity of the penile shaft. Only in 5% of cases penile cancer takes origin from the proximal part of the penile shaft.[1-3] Macroscopically, the lesion may be vegetating in 38% of cases, ulcerated in 52% and nodular in 10%.[4] There is often a significant delay from the beginning of symptoms to diagnosis, which may be a year or more in 15%-50% of cases.[5]

The primary tumor progressively infiltrates penile structures, presenting a high tendency to spread through lymphatic pathways to superficial inguinal, deep inguinal and pelvic lymph nodes. Only in the most advanced lymph node involvement is it possible to find distant metastases.

Regional (inguinal and/or pelvic) lymph node involvement is the most important and significant factor predicting survival in patients with penile cancer. In patients with localized disease, the most relevant prognostic aspect is the identification of clinical and/or pathological factors able to predict the disease progression to regional lymph node metastases.

Distant metastases

Distant metastases to lung, liver, bone or brain are present only in 1%-10% of patients. They are rare in patients without lymph node involvement.[1,5-7] This category of patients is characterized by a particularly unfavorable prognosis, with mean survivals approaching 7-10 months,[6,8] maximally 22 months.[8]

Regional lymph node metastases

The presence of metastases in regional lymph nodes is the main factor able to predict an unfavorable prognosis for patients with penile cancer. At first diagnosis, about 28%-64% of patients present with clinically palpable lymph nodes.[9] Nevertheless, only in 47%-85% of cases enlarged inguinal lymph nodes are due to metastases.[10-12] In the remaining cases, this feature is caused by an inflammatory process due to the presence of infection in the primary tumor. In patients with metastases to inguinal lymph nodes concomitant pelvic lymph node metastases are present in 22%-56% of cases.

The 1997 TNM classification distinguishes the following nodal stages: N0 - no lymph node involvement; N1 - single metastasis in a superficial inguinal node; N2 - multiple or bilateral superficial inguinal metastases; N3 - deep inguinal and/or pelvic metastases (Table 1).[13]

Table 1: TNM classification, 1997[13]: disease extension to regional lymph nodes

Stage (N)	Definition
N0	No evidence of regional lymph node metastasis
N1	Metastasis in a single, superficial inguinal lymph node
N2	Metastases in multiple or bilateral, superficial lymph nodes
N3	Metastasis in deep inguinal and/or pelvic lymph node

This classification can be applied defining both the clinical and the pathological stage of disease of patients who need an inguinal and/or pelvic lymph node dissection.

Considering the clinical stage of regional lymph nodes, 5-year cause-specific survival in the main published series ranges from 75% to 93% in patients with cN0 disease; 40%-70% in cN1; 33%-50% in cN2; and 20%-34% in cN3.[14] Table 2 summarizes literature data on penile cancer patients' survival according to clinical stage.

Table 2: 5-year survival (%) of penile cancer patients according to clinical lymph node stage

Author	cN0	cN+	cN1	cN2	cN3
Kamat et al. 1993[15]	75	NR	40	39	NR
Horenblas et al. 1993[10]	93	50	57	50	17
Kulkarni and Kamat, 1994[16]	81	52	NR	NR	NR
Lopes et al. 1996[17]	56	NR	49	67	19
Villavicencio et al. 1997[18]	NR	NR	71	33	NR
Bezerra et al. 2001[19]	70	NR	71	78	34
Lopes et al. 2002[20]	56	NR	26.7	62.7	18.2
Novara et al. 2007[14]	80	38	57	37	25

NR: not reported

Pathological stage has an undoubtedly higher relevance than clinical stage of regional lymph nodes in the prediction of prognosis. While patients classified as pN0 after inguinal lymph node dissection have 5-year cancer-specific survival rates of 85%-100%, patients with any lymph node involvement (pN+) have 5-year cancer-specific survival rates of 16%-45%.[18,19] Table 3 summarizes the 5-year survival rates after inguinal and/or pelvic lymph node dissection.

Table 3: 5-year cancer-specific survival (%) in patients with pathologically staged regional lymph node involvement

Author	5-year cancer-specific survival (%)	
	Histologically node negative (pN0)	Histologically node positive (pN+)
Beggs and Spratt, 1964[21]	72.5	19.3
Johnson and Lo, 1984[22]	74	
Srinivas et al. 1987[23]	85	32
Pow-Sang et al. 1990[24]	80	62.5
Ravi, 1993[25]	95	53
Ornellas et al. 1994[9]	87	29
Lopes et al. 1996[17]	70	40.3
Villavicencio et al. 1997[18]	74	16
Derakhshani et al. 1999[26]	88.4	28.6
Bezerra et al. 2001[19]	89.5	44.9
Lont et al. 2006[27]	94	60

Dai et al. 2006[28]	77.7	33.6
Pandey et al. 2006[29]	95.7	51.1
Ornellas et al. 2008[30]	96*	35*

* 10-year disease-free survival

The prognosis of patients with lymph node metastases may vary according to different variables, such as the number of positive lymph nodes, uni- or bilateral inguinal extension, pelvic node involvement and the presence of lymph node capsular involvement.[10,23,25,29]

Only some of this information is taken into account in the TNM classification (1997) (Table 1).[13] pN1 patients have a 5-year cancer-specific survival of 79%-89%; pN2 patients 7%-60%; pN3 patients 0-7% (Table 4).[14,29]

Table 4: 5-year cancer-specific survival (%) of penile cancer patients according to pathological lymph node involvement

Author	pN0	pN+	PN1	pN2	pN3
Srinivas et al. 1987[23]	85	32	NR	NR	NR
Ornellas et al. 1991[31]	87	29	NR	NR	NR
Horenblas et al. 1993[10]	100	NR	79	17	NR
Ravi, 1993[25]	95	NR	86	60	0
Kulkarni and Kamat, 1994[16]	91	NR	NR	NR	NR
Brkovic et al. 1997[32]	90	NR	80	NR	17
Pow-Sang et al. 1990[24]	92	NR	80	NR	17
Pandey et al. 2006[29]	95	51	NR	21	0
Novara et al. 2007[14]	94	29	89	7	0

The 1997 TNM classification does not take into account the prognostic impact of the number of positive regional nodes. This parameter has been widely considered and there is a negative correlation between the number of metastatic lymph nodes and 5-year cancer-specific survival. Specifically, most authors documented a significant worsening of survival in the presence of metastasis in more than 2 regional lymph nodes (Table 5).

Table 5: 5-year cancer-specific survival of patients with penile cancer according to the number of metastatic lymph nodes

Author	Patients (n)	5-year cancer-specific survival (%)	
		≤2 nodes positive	>2 nodes positive
Johnson and Lo, 1984[22]	22	85	13
Srinivas et al. 1987[23]	119	82	20
Fossa et al. 1987[33]	18	88	33
Fraley et al. 1989[34]	31	88	7
Horenblas et al. 1993[10]	110	67	39

In 1993 Ravi et al. proposed using a numerical cut-off to differentiate the prognosis of patients with regional lymph nodes from penile cancer. In a series of 98 patients they reported a 5-year cancer-specific survival rate of 81% in patients with ≤3 lymph nodes involved and of 50% in cases with more than 3 nodes involved.[25] More recent data from the same center showed 5-year cancer-specific survival rates of 75% in patients with 1-3 metastatic lymph nodes, 8.4% in patients with 4-5 metastatic nodes and 0 in those with more than 5 nodes involved. In this last category of patients, the estimated 3-year survival rate was only 12.5%. The number of metastatic nodes was an independent prognostic factor for patients with penile cancer involving the lymph nodes. Specifically, the presence of metastasis in 4-5 nodes caused a death risk increase of 4.5 times (hazard ratio (HR) 4.598 - 95% confidence interval (CI) 1.256 - 16.830) compared to the presence of metastases in a lower number of nodes. Moreover, the involvement of more than 5 nodes further increased the risk to 12 times (HR 12.06 - 95% CI 2.525 - 57.59).[29]

A further prognostic parameter which has not been correctly considered by the TNM classification is pelvic lymph node extension. In fact, the N3 category includes both patients with deep inguinal and pelvic node involvement. Patients with pelvic node metastases have a significantly lower survival than patients with inguinal metastases only. Pandey et al. recently reported a 5-year survival of 64% for patients with inguinal metastases only and 0 in those with disease extending to pelvic nodes. In this last category only 28% of patients were alive after 2 years and all patients died within 3 years of follow-up. In multivariate analysis, the presence of pelvic node metastases increased the risk of death by 31 times (HR 31.68 – 95% CI 6.773 – 32.62) and predicted a very poor survival rate (Table 6).[29]

Table 6: 5-year survival (%) of penile cancer patients with pelvic node metastases

Author	Patients (n)	5-year cancer-specific survival (%)
de Kernion et al. 1973[35]	2	50
Cabanas, 1977[36]	5	40
Puras et al. 1978[37]	7	28.5
Srinivas et al. 1987[23]	11	0
Pow-Sang et al. 1990[24]	3	66
Kamat et al. 1993[15]	6	33
Horenblas et al. 1993[10]	2	0
Ravi, 1993[25]	30	0
Lopes et al. 2000[38]	13	38
Pandey et al. 2006[29]	21	0

As in other urological tumors, in penile cancer extranodal metastatic extension also has a negative prognostic significance. The possible negative prognostic impact of this variable was initially reported in 1987 by Srinivas et al.[23] and subsequently confirmed by Ravi in 1993.[25] In the 98 patients with lymph node metastases studied by Ravi, extranodal metastatic infiltration was described in 17% of cases. Specifically, all patients had >4 cm metastases and only one patient (5.8%) was alive after 5 years.[25] More recent data demonstrated that patients with extranodal metastatic involvement had 2-, 3- and 5-year survival rates of 58%, 17.8% and 8.9%, respectively. These figures are significantly lower than those observed in patients without extranodal metastatic infiltration, that are 98%, 95%, and 90%, respectively (Fig. 1). The finding of extranodal metastatic extension was associated with an increased risk of death of 9 times (HR 9.206 – 95% CI 2.598 – 32.62).[29]

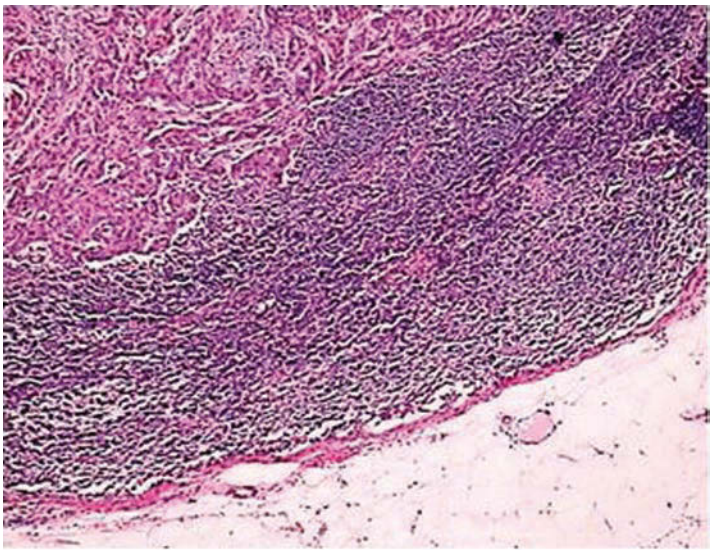

Fig. 1: *Penile cancer metastasis in an inguinal lymph node showing the perinodal capsule surrounding the neoplastic tissue without any perinodal extension.*

Prognostic factors of the primary tumor

Occult micro-metastases can be present in 12%-24% of patients with penile cancer and nonpalpable lymph nodes.[5] This was recently confirmed with the finding of lymph node disease progression in 9%-21% of patients on surveillance for clinically nonpalpable inguinal nodes (cN0).[3,7] Of the patients who progressed during surveillance, 50% did so within 6 months, 77% within 1 year and 100% within 2 years after treatment of the primary tumor.[3]

Early bilateral inguinal lymph node dissection can significantly improve prognosis in patients with inguinal micrometastases. Nevertheless, this kind of surgery has major complications in 24%-87% of cases which can lead to death in 3%.[39] For this reason, inguinal lymphadenectomy might be considered overtreatment in 75-90% of cases, where micrometastases are not present. The pathological and molecular features of the primary tumor might help to predict regional lymph node involvement. Several variables have been described which are able to predict regional lymph node involvement in penile cancer patients (Table 7).

Table 7: Variables of the primary tumor able to predict inguinal lymph node involvement

- Clinical factors
  - Age
  - Primary tumor clinical stage (cT)
- Pathological factors
  - Histological subtype
  - Primary tumor pathological extension (pT)
  - Histological grade of the primary tumor (G)
  - Percentage of poorly differentiated tumor
  - Growth pattern of the primary tumor
  - Lymphatic and/or venous embolization
  - Primary tumor thickness
  - HPV 16 or 18 infection
- Molecular factors
  - p53
  - E-cadherin
  - Matrix metalloproteinase (MMP)-2 or 9

Clinical factors

▪ Age

There is controversy about the influence of the patient's age at diagnosis on the risk of disease progression to regional lymph nodes. In patients ≤50 years old the percentage of lymph node metastases is 39%-58%, similar to the rate of 48%-52% in patients >50 years old.[20,40,41] In 1996 Lopes et al. reported significantly different 5-year survival rates among patients ≤40, 41-60, and >60 years old, namely 64.5%, 59.6%, and 38.4%, respectively (p=0.05).[17] More recently the same group found significant differences in

univariate analysis between patients ≤50 and >50 years old, namely 61% and 41%, respectively (p=0.002).[20] On the contrary, Lont et al. reported 5-year survival rates of 78% in patients ≤60 and 85% in those >60 years old (p=0.28).[27] Recent data showed that age is an independent variable able to predict overall survival (HR 2.3 – 95% CI 1.0 – 5.1), just like the presence of lymph node metastases (HR 3.2 – 95% CI 1.8 – 5.6) and pathological stage of the primary tumor (HR 1.9 – 95% CI 1.0 – 3.6).[42]

- **Clinical stage of the primary tumor**

The latest version of the TNM staging system classifies penile cancer in carcinoma in situ (Tis), carcinoma infiltrating the subepithelial tissue (T1), corpora cavernosa or urethral corpus spongiosum (T2), urethra (T3), prostate and adjacent structures (T4).[13] This classification is more easily applied to define the pathological extension than the clinical stage of the tumor.[12] For this reason, the 1978 TNM version is more often used to define the clinical stage of disease. According to this classification, penile cancer might be classified into exophytic lesions ≤2 cm (T1); superficial lesions of 2 to 5 cm or *with minimal depth invasion* (T2); lesions >5 cm or *with deep invasion* (T3); neoplasms infiltrating adjacent structures (T4).[43] Even though the major series report that the percentage of lymph node metastases increases with the clinical stage, only in the multicentric experience of the Italian Uro-Oncologic North-Eastern Group (GUONE) this clinical parameter turned out to be related to the risk of groin lymph node involvement in univariate analysis. Specifically, they found a percentage of inguinal metastases of 25% in cT1, 34% in cT2, and 66% in cT3-4. Nevertheless, multivariate analysis showed that this parameter had no independent prognostic meaning, as the only prognostic factor able to independently predict inguinal metastases was the finding of palpable or fixed inguinal lymph nodes.[3] More recently others reported lymph node metastasis rates of 34%-42% in cT2 and 48%-52% in cT3-4.[40,41]

In terms of 5-year survival, the only study showing a statistically significant difference in primary tumor clinical stages was the one published in 1994 by Horenblas et al. showing 5-year survival of 94% in cT1, 59% in cT2, 52% in cT3-4.[44] Globally, there is an increase of lymph node involvement in patients with higher clinical stage, more so if we compare pT1 versus pT2-T3.

Pathological factors

- **Histological subtype of the primary tumor**

Verrucous carcinoma of the penis is characterized by an exceptionally low tendency to metastasize to inguinal lymph nodes. On the contrary, basaloid SCC of the penis has an exceptionally high tendency to involve regional lymph nodes. The typical SCC has an intermediate behavior. Specifically, the percentage of lymph node metastases has been reported to be 0 in verrucous carcinoma, 100% in basaloid carcinoma, and 30% in SCC. In the presence of this last histological subtype, regional lymph node involvement is mainly related to other pathological factors, such as pathological stage (>pT1), and depth of invasion (>6 mm).[28] Most published data refer to typical SCC, representing the most frequent subtype of penile cancer. Hence, it is always preferred to have adequate histological characterization of the primary tumor.

- **Primary tumor pathological extension (pT)**

In patients with nonmetastatic disease, the prognostic importance of the pathological stage of the primary tumor is related to the possibility to predict the presence of occult metastases in non-palpable inguinal lymph nodes. There is an unequivocally direct correlation between the local extension of the primary tumor and the risk of involvement of regional nodes (Table 8).

Table 8: Regional lymph node involvement rates in patients with penile cancer according to the pathological stage of the primary tumor (pT)				
Author	**Patients (n)**	**Regional lymph node involvement (%)**		
		pT1	**pT2**	**pT3**
Narayana et al. 1982[45]	219	10	56	
Mc Dougal et al. 1986[46]	65	0	67	
Bouchot et al. 1989[11]	45	11	61	
Pettaway et al. 1991[47]	-	6	40	
Solsona et al. 1992[48]	66	4	64	
Horenblas et al. 1993[10]	110	14	52	
Lopes et al. 1996[17]	145	45	63.6	44.7
Theodorescu et al. 1996[49]	42	58	66.7	-
Heyns et al. 1997[50]	35	0	50	
Pizzocaro et al. 1997[12]	-	-	82	100
Villavicencio et al. 1997[18]	81	11	38	
Solsona et al. 2001[51]	37	11	63	
Slaton et al. 2001[52]	48	0	55	
Lopes et al. 2002[20]	82	-	60.7	41.7
Ficarra et al. 2005[3]	175	20	43	70
Guimaraes et al. 2006[40]	112	38	57	
Campos et al. 2006[41]	125	32	52	
Dai et al. 2006[28]	64	18%	53%	

Recently, Lont et al. reported a 5-year survival of 95% in patients with pT1 penile cancer, significantly higher than the 74% recorded for patients with pT2-3 disease (p= 0.003). In this series analyzing 176 patients, pathological stage of the primary tumor turned out to be an independent prognostic factor for survival (HR 4.0 - 95% CI 1.1 - 14.0), together with vascular embolization (HR 4.5 - 95% CI 1.4 - 14.6) and regional lymph node metastases (HR 7.0 - 95% CI 2.8 - 17.6).[27] Different results had been previously reported. Bezerra et al. analysed data from 82 patients, reporting 5-year cancer-specific survival rates of 80% in pT1, 62% in pT2, 64% in pT3, without any statistically significant difference.[19] In 2002 Lopes et al. reported 5-year cancer-specific survival rates of 57% in pT1, 52% in pT2 and 49% in pT3.[20]

▪ Histological grading (G)

The histological grading of penile cancer is usually given according to the classification published by Broders in 1921, distinguishing grade 1 or well differentiated, grade 2 or moderately differentiated, and grade 3 or poorly differentiated tumors.[53] Also the histological tumor grade has been demonstrated to be an important factor able to predict the metastatic involvement of regional lymph nodes (Table 9).

Table 9: Percentage of groin lymph node metastases in patients with penile cancer according to the histological tumor grade (G)				
Author	**Patients (n)**	**Regional lymph node involvement (%)**		
		G1	**G2**	**G3**
Fraley et al. 1989[34]	58	30	70	60
Solsona et al. 1992[48]	66	20	65	86
Horenblas et al. 1993[10]	110	29	46	82
Lopes et al. 1996[17]	145	47.5	64.1	66.7
Theodorescu et al. 1996[49]	42	30.8	80.8	
Heyns et al. 1997[50]	35	4	79	100
Villavicencio et al. 1997[18]	81	0	38.5	80
Solsona et al. 2001[51]	37	10	69	75
Slaton et al. 2001[52]	48	20	42	
Lopes et al. 2002[20]	82	46	62	
Ficarra et al. 2005[3]	175	14	47	
Guimaraes et al. 2006[40]	112	48	50	
Campos et al. 2006[41]	125	44	44.4	
Dai et al. 2006[28]	64	20.8	32.3	47.1

In 2001 Slaton et al. used the Broders classification together with two further parameters: the percentage of poorly differentiated tumor and nuclear grading.[52] On the basis of nuclear size, nucleolar polymorphism and nucleus/cytoplasm ratio, it was possible to classify penile cancer into 3 different nuclear grades. The study showed that only a cut-off percentage ≤ or >50% of poorly differentiated tumor was related to significantly different percentages of inguinal metastases. No significant differences were observed for Broders or nuclear grading, but the study only analyzed 48 patients.[52]

Data related to 5-year cancer-specific survival do not show significant differences between patients with different histological grades. Only Horenblas et al. showed significantly different 5-year survival rates in patients with grade 1 and grade 3 tumors, 79% and 47%, respectively.[44] More recent studies reported 5-year cancer-specific survival rates of 53%-83% in well differentiated tumors and 47%-74% in moderately and poorly differentiated ones.[19,20,27] In 2008 Ornellas et al. reported a statistically significant difference in cancer-specific survival of patients with well and moderately differentiated tumors ($p<0.0001$) compared with poorly differentiated tumors ($p=0.006$).[30]

▪ Solsona et al. and European Association of Urology (EAU) risk groups

The risk of regional lymph node involvement can be estimated in a more accurate fashion combining the information provided by the pathological stage and the histological grading of the primary tumor (Table 10).

Table 10: Stratification of patients with penile cancer combining the information provided by the primary tumor pathological stage (pT) and histological grade (G)			
Risk group	**Solsona et al. classification[48]**	**EAU classification[2]**	**Ornellas et al.[30]**
Low	Tis/Ta/T1G1	Tis - TaG1-2 - T1G1	T1G1, T1G2
Intermediate	T1G2-3 or T2-3G1	T1G2	T2-3G1, T2-3G2
High	T2-T3G2-3	T2-T3 or G3	T1-2G3, T4G1-3

In 1992 Solsona et al. proposed a stratification of penile cancer patients into 3 groups with different risk for inguinal node involvement, combining the pathological stage and histological grade of the primary tumor. Patients with pT1/grade 1 disease were classified as low risk of node involvement; those with pT1/grade 2-3 and pT2/grade 1 as intermediate risk; those with pT2/grade 2-3 or ≥pT3 as high risk. The percentage of node metastases in the 3 groups was 0, 36.4%, and 80%, respectively.[48] This classification was validated in 2001 by the same group in a prospective series of 37 patients where the percentage of inguinal metastases was 0 in low risk, 33% in intermediate risk and 83% in high risk groups.[51]

The ability of the Solsona et al. classification to stratify patients with penile cancer according to the different risk of inguinal lymph node metastases was recently confirmed in an Italian multicentric study analyzing 175 patients observed between 1980 and 2002. In this study, lymph node metastases were observed in 4% of low risk, 29.1% in intermediate risk and 53.5% in high risk patients ($p<0.001$).[3]

Similar to what was proposed by Solsona et al. in 1992, the expert panel drafting the EAU guidelines proposed a slightly different classification. Specifically, patients were classified as low risk in case of pTis, pTaG1-2, pT1G1 disease; as intermediate risk in case of pT1G2 tumors; as high risk in case of ≥pT2 or G3 cancer.[2] The risk of inguinal metastases according to the EAU classification was 4% in low risk, 34.8% in intermediate risk, 45.8% in high risk patients.[3]

Nevertheless, a recently published study by Novara et al. showed that both the Solsona et al. and the EAU risk groups have a low prognostic accuracy. In this study the receiver operating characteristic (ROC) curves showed values of 0.697 (95% CI 0.618 - 0.777) for the Solsona et al. classification and 0.632 (95% CI 0.548 - 0.715) for the EAU one.[54]

Ornellas et al. recently proposed a new classification of penile cancer patients into 3 different risk groups according to primary tumor pathological stage and histological grade. Patients were defined as low risk in case of T1G1-2 tumor; as intermediate risk in T2G1-2 or T3G1-2 disease; as high risk in case of T1-3G3 or T4G1-3 cancer. The authors observed a significant difference in terms of 10-year cancer-specific survival between low and intermediate-risk patients ($p=0.01$) and between intermediate and high-risk patients ($p<0.001$).[30]

▪ Lymphatic and venous embolization

The prognostic significance of lymphatic and venous embolization was initially reported by Lopes et al. in 1996 in a series of 145 patients who had undergone penile amputation and inguinal lymph node dissection.[17] In this study, lymphatic embolization was defined as nests of carcinomatous cells in a lumen with thin walls, without smooth muscle fibers or red blood cells. The same condition with red blood cells or smooth muscle fibres was considered as venous embolization (Fig. 2).[17,19,55]

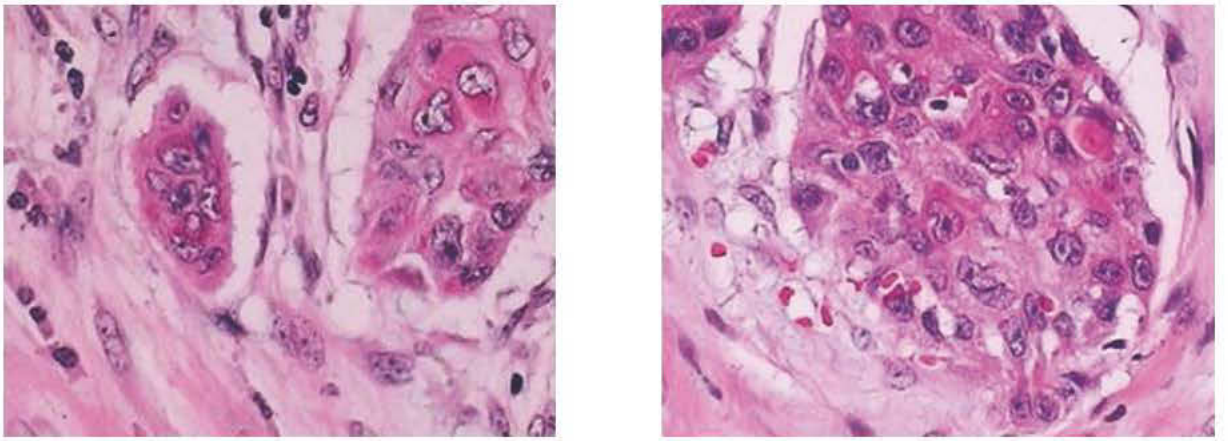

Fig. 2: *A) Lymphatic embolization is defined as nests of carcinomatous cells in a lumen with thin walls, without smooth muscle fibers or red blood cells. B) The same condition with red blood cells or smooth muscle fibers is considered as venous embolization.*

Patients without lymphatic embolization in the primary tumor have lymph node metastases in 17%-30.6%.[20] In contrast, patients with lymphatic embolization have lymph node metastases in 62%-83.3%. In all published series this difference is statistically significant. Similarly, patients with venous embolization have lymph node metastases in 69%-89%, significantly more than the 24%-43.8% reported in patients without venous embolization (Table 11).

Table 11: Inguinal lymph node involvement rates in penile cancer patients according to the presence or absence of lymphatic or venous embolization in the primary tumor

Author	Patients (n)	Regional lymph node involvement (%)			
		Lymphatic embolization		Venous embolization	
		Absent	Present	Absent	Present
Lopes et al. 1996[17]	145	30.6	63.5*	43.8	77.8*
Lopes et al. 2002[20]	82	21.4	65.2*	42	70*
Ficarra et al. 2002[55]	30	22	100*	25	100*
Ficarra et al. 2005[3]	175	22.5	83.3*	24	89*
Guimaraes et al. 2006[40]	112	26	65*	43	69*
Campos et al. 2006[41]	125	17	62*	34	69*

Venous and lymphatic embolization are two important factors able to independently predict the presence of inguinal lymph node metastases.[3,20]

The embolization of peritumoral lymphatic vessels has a negative impact also on 5-year survival of penile cancer patients. In 2001, Bezerra et al. reported 5-year survival rates of 88% in patients without lymphatic embolization and 55% in those with this feature (p=0.004).[19] Similar results were reported by Lopes et al. in 2002. These authors reported 5-year cancer-specific survival in 65% of patients without and 41.5% in those with lymphatic embolization (p=0.004).[20] Nevertheless, this parameter was not an independent predictor of cancer-specific survival in multivariate analysis.

Concerning the impact of venous embolization on survival, the differences reported were not statistically significant in univariate analysis. Specifically, Bezerra et al. reported 5-year sur-

vivals of 73.7% in patients without and 52% in those with venous embolization[19] while Lopes et al. in 2002 reported 5-year survivals of 56% and 38%, respectively, in those without and with venous embolization.[20] Lont et al. reported 5-year cancer-specific survival rates of 83% in patients without and 69% in those with venous embolization.[27]

▪ Tumor thickness

Tumor thickness is usually measured from the top of the tumor to the deepest tumor cell and reported in mm.[52] Its ability to predict node involvement is controversial. Some authors reported lymph node metastasis rates significantly higher in patients with tumor thickness >5 mm,[3,17,41] others recorded statistically non-significant differences.[20,40,52] The percentage of metastatic nodes reported in patients with tumor thickness ≤5 mm ranged from 22% to 44%, and with tumor thickness >5 mm it was 38-57%.

Velazquez et al. recently studied 134 patients with tumor thickness of 5-10 mm and in this group of patients they demonstrated that high-grade tumors with perineural involvement were those with the highest risk of node involvement.[56]

Five-year cancer-specific survival rates are reported to be 56%-78% in patients with tumor thickness ≤5 mm and 48%-64% in those >5 mm (Table 12).

Table 12: Lymph node metastasis rates and 5-year cancer-specific survival in patients with penile cancer according to tumor thickness

Author	Patients (n)	Lymph node involvement (%)		5-year survival (%)	
		Thickness ≤5 mm	Thickness >5 mm	Thickness ≤5 mm	Thickness >5 mm
Lopes et al. 1996[17]	145	33	57.7	64	52
Bezerra et al. 2001[19]	82	-	-	78	64
Slaton et al. 2001[52]	48	36	38	-	-
Lopes et al. 2002[20]	82	35	55	56.7	48.7
Ficarra et al. 2005[3]	175	22.2	50.5	-	-
Guimaraes et al. 2006[40]	112	44.4	51.3	-	-
Campos et al. 2006[41]	125	28.6	49.4	-	-

▪ Growth pattern

According to Cubilla et al. the growth pattern in penile cancer can be classified in verrucous, superficial and vertical patterns.[57] In 1997 Villavicencio et al. reported significant correlations between tumor growth pattern and inguinal node involvement in penile cancer patients who had undergone inguinal lymphadenectomy. Specifically, they reported inguinal metastases in 0 patients with verrucous tumors, in 35% of those with superficial and 100% of those with vertical growth patterns (p=0.0009). Similarly, they reported significantly better survival in patients with superficial compared to those with vertical growth tumors (p=0.0004). In contrast, survival was not significantly different in patients with verrucous compared to those with superficial growth pattern tumors.[18]

Pizzocaro et al. highlighted the significance of tumor growth pattern in the prediction of lymph node metastases in cT1 patients. In this subgroup node involvement was 9.4% in exophytic tumors and 30.7% in endophytic ones.[12] Using Cubilla's classification, Ficarra et al. did not report significant differences in the percentages of node metastases found in patients with superficial compared to vertical growth pattern tumors.[3]

An interesting literature contribution was provided in 2006 by Guimaraes et al. [40] These authors classified their patients according to the classifi-

cation proposed by Anneroth et al.[58] and Bryne et al.[59] for oral cavity squamous cell cancers. The pattern of invasion expresses the tumor-host tissue relationship, demonstrating the infiltrative tumor characteristics. This pattern was defined as infiltrating (invasion in blocks of small solid strands of cells broadly infiltrating the organ's stroma) and pushing infiltration (tumor cells invading large cell blocks with well-defined tumor-host interfaces). Patients with an infiltrating pattern of invasion had node metastases in 64.6%, significantly higher than the 23% reported in patients with a pushing pattern of invasion ($p<0.001$). This pathological parameter was an independent predictor of node involvement (HR 4.18 - 95% CI 1.5 - 11.3), together with lymphatic embolization (HR 3.95 - 95% CI 1.5 - 10.4) and clinical stage of lymph nodes (HR 3.85 - 95% CI 1.4 - 10).[40]

- **Human papillomavirus (HPV) infection**

In contrast to the established role of HPV as a risk factor, little is know about its prognostic significance in penile SCC.

In 1992 Wiener et al. documented no significant difference in survival between patients with HPV positive and those with HPV negative tumors.[60] Bezerra et al. in 2001 hypothesized that the presence of HPV DNA in the primary tumor could have a prognostic impact. Their study showed node metastases in 73.8% of HPV negative and 26.2% of HPV positive tumors, but this difference was not statistically significant ($p=0.38$). Also, they did not observe significant survival differences between the two groups of patients.[19] Similar results were reported by Lopes et al. in a series of 82 patients who had undergone penectomy and inguinal lymph node dissection. In this series HPV positive tumors had inguinal metastases in 44% of cases, compared to 54.4% in HPV negative tumors. Moreover, 5-year cancer-specific survival rates were 44.7% and 53.1%, respectively ($p= 0.271$).[20]

A more recent study was conducted in the Netherlands on 171 patients treated for penile cancer between 1963 and 2001. Positive lymph nodes were found in 71% of HPV negative patients and 29% of HPV positive ones ($p=0.90$).[27] Also Protzel et al. did not find any correlation between HPV DNA and node involvement.[61]

Concerning cancer-specific survival, Lont et al. reported 5-year cancer-specific survival rates of 92% for HPV positive and 78% for HPV negative patients ($p=0.03$). In this study, HPV was able to predict survival independently from primary tumor pathological stage, venous embolization and regional lymph node involvement.[27] Currently, there is no scientific explanation why HPV negative patients should have lower cancer-specific survivals.

- **Koilocytosis**

In 2007 some authors evaluated the prognostic significance of koilocytosis, defined by huge halos around cell nuclei.[42,62] Its detection is pathologist dependent. It is not a significant predictor of regional node involvement or survival of penile cancer patients. Specifically, de Paula et al. reported lymph node metastases in 63.8% of cases with and 36.2% of cases without koilocytosis ($p=0.95$). Also 3-year cancer-specific survival rates were not significantly different, 32% versus 61.5%.[62]

- **Ploidy**

Gustaffson et al. reported on 26 patients with invasive penile cancer with a mean follow-up of 29 months and found that high-grade tumors tended to be non-diploid. However, ploidy status did not add significant information concerning the risk of metastatic disease.[63] In 1992 Yu et al. performed ploidy analysis on tumors from 11 patients with penile cancer and found that 7 (64%) were diploid and 4 (36%) were aneuploid. At follow-up, 6 of the patients were alive, all with diploid tumors and no inguinal metastasis. Five of the patients died of disease, all had node metastases, and 4 had non-diploid tumors.[64] More recently, Hall et al. concluded that DNA flow cytometry does not add prognostic information to that obtained by pathologic assessment in patients with invasive penile carcinoma.[65]

Nomograms

Several nomograms predictive of cancer-specific or disease-free survival probabilities have been developed in urological oncology in the recent past. Nomograms are mathematical predictive models integrating prognostic information coming from the main clinical and/or pathological variables, improving their prognostic accuracy. In 2006, three nomograms were published with the aim to predict inguinal lymph node involvement[4] and 5-year cancer-specific survival of penile cancer patients.[66]

The first one[4] was generated to predict node involvement in penile cancer patients, integrating data from 8 different clinical and pathological variables (clinical inguinal lymph node stage, pathological tumor thickness, growth pattern, histological grade, lymphatic and/or venous embolization, corpora cavernosa infiltration, corpus spongiosum and/or urethral infiltration) (Fig. 3).

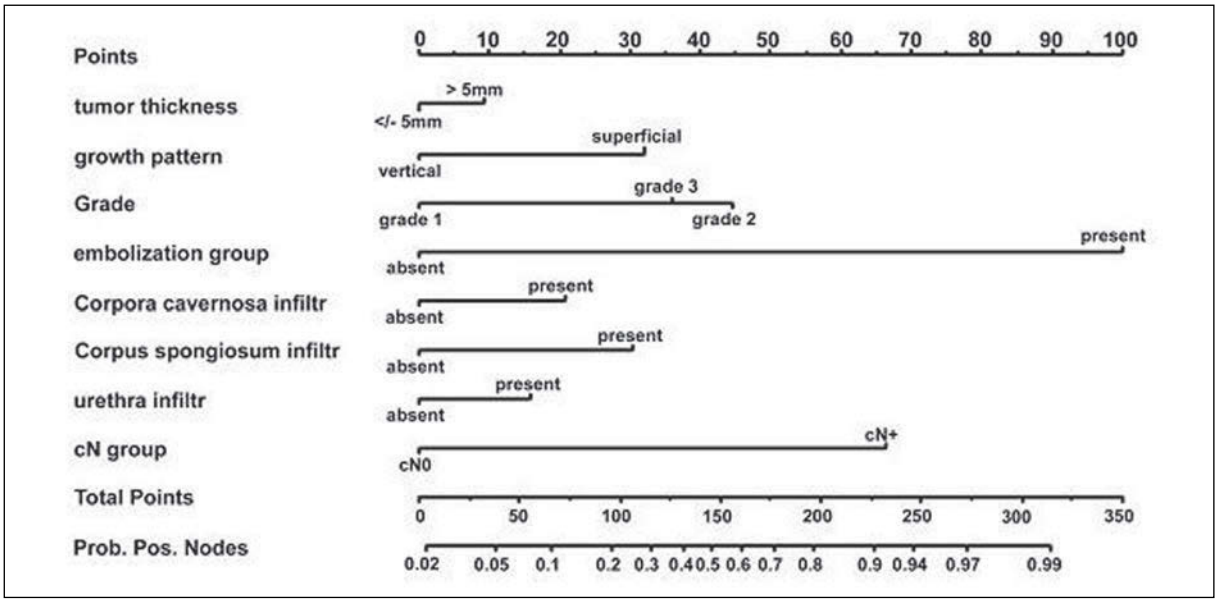

Fig. 3: *Nomogram predicting the probability of inguinal lymph node metastases*

Instructions for physicians: *Locate the tumor thickness on the tumor thickness axis. Draw a line straight upward to the Points axis to determine the number of points received for tumor thickness. Repeat this process for the remaining axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate the sum on the Total Points axis. Draw a line straight down to find the 5-year cancer specific survival of the patient.*

Instructions to patient**:** *"Mr. X, if we had 100 men exactly like you, we would expect the predicted percentage from the nomogram to be free of disease specific death in 5 years, assuming no one died of another cause."*

This integrated staging system demonstrated excellent prognostic accuracy, with an AUC (area under the curve) of the ROC curves of 0.876 and good calibration.[4] Currently, the use of this nomogram in clinical practice is potentially limited by the lack of external validation.[14]

In the same year the Italian Uro-Oncologic North-Eastern Group (GUONE) proposed two nomograms able to estimate 5-year cancer-specific survival in penile cancer patients.[66] In the first model, the 5-year cancer-specific survival probabilities were estimated according to clinical stage of the inguinal lymph nodes and the pathological findings of the primary tumor after partial or total penectomy (tumor thickness, growth pattern, grade, venous and/or lymphatic embolization, corpora cavernosa infiltration, corpus spongiosum infiltration and urethra infiltration). The concordance index of this first model was 0.728. This model, which also showed good calibration, may be used to estimate survival probabilities after surgery of the primary tumor, regardless of locoregional lymph node management (Fig. 4).

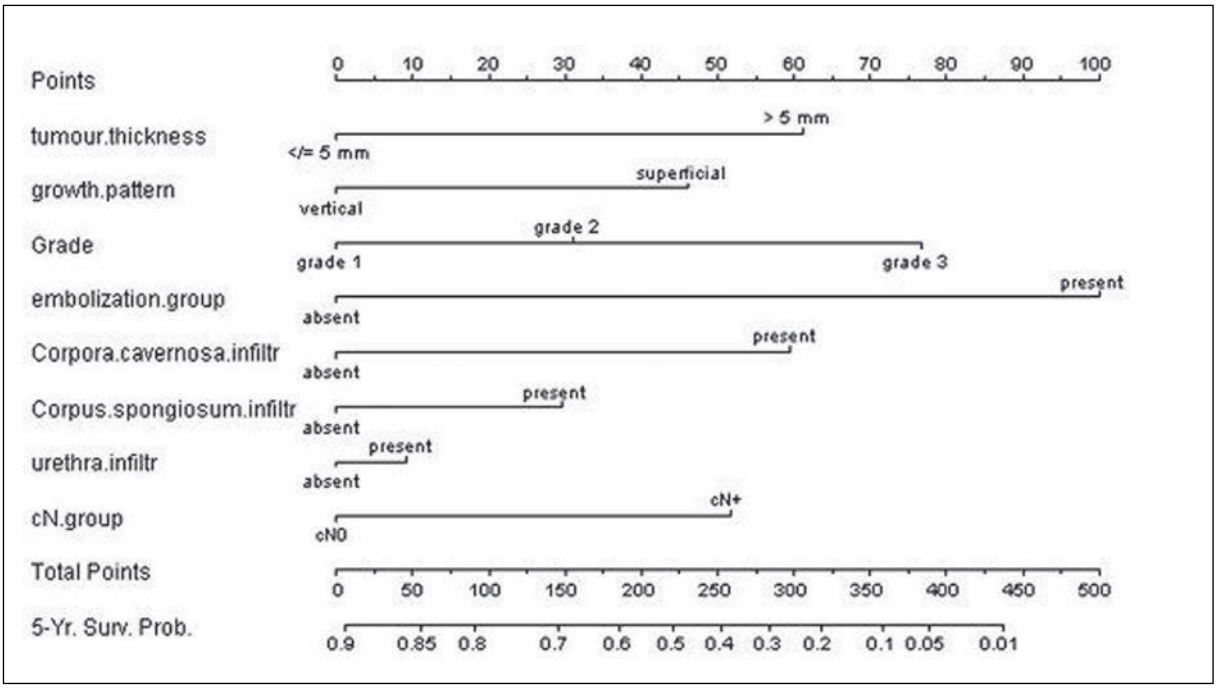

Fig. 4: *Nomogram predicting 5-year cancer-specific survival according to pathological findings of primary tumor and clinical stage of lymph nodes.*

***Instructions for physicians*:** *Locate the tumor thickness on the tumor thickness axis. Draw a line straight upward to the Points axis to determine the number of points received for tumor thickness. Repeat this process for the remaining axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate the sum on the Total Points axis. Draw a line straight down to find the 5-year cancer specific survival of the patient.*
***Instructions to patient*:** *"Mr. X, if we had 100 men exactly like you, we would expect the predicted percentage from the nomogram to be free of disease specific death in 5 years, assuming no one died of another cause."*

In the second model, the 5-year cancer-specific survival probabilities were estimated according to the pathological findings of the primary tumor after partial or total penectomy and the pathological stage of inguinal lymph nodes after lymphadenectomy. This model may be useful for patients undergoing either inguinal lymphadenectomy (pN0/pN+) or watchful waiting (Nx) to plan the most appropriate follow-up schedule and to identify patients who need adjuvant therapy to improve their outcome (Fig. 5).[66]

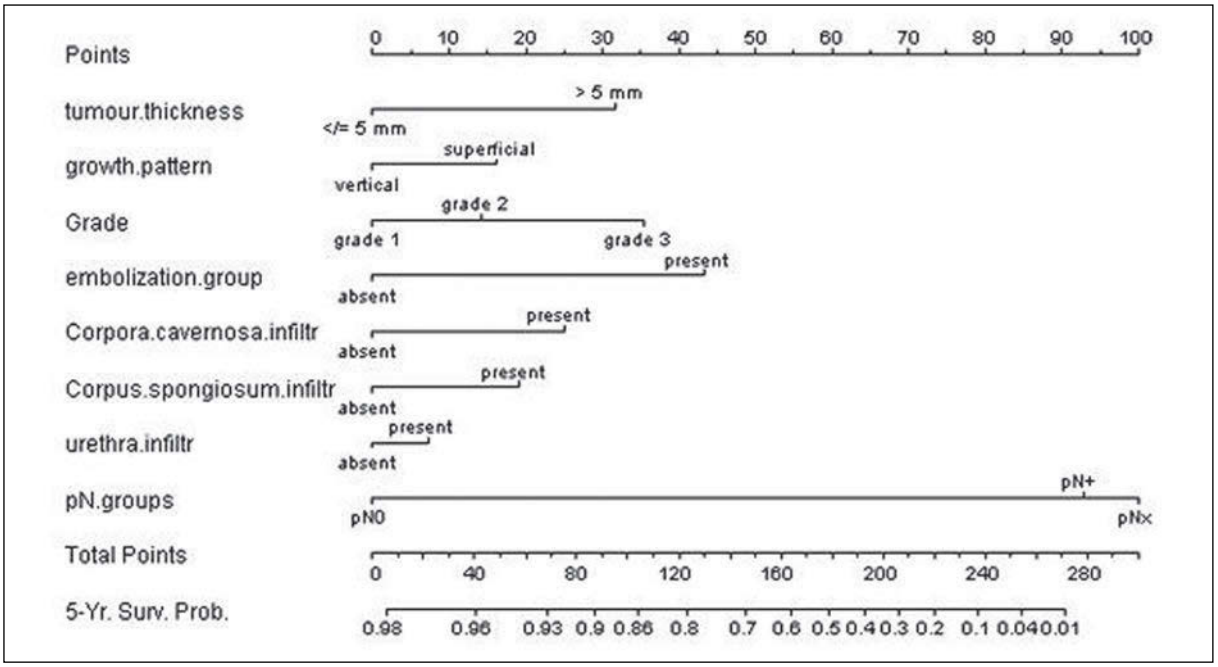

Fig. 5: *Nomogram predicting 5-year cancer-specific survival according to pathological findings of primary tumor and pathological stage of lymph nodes.*

Instructions for physicians: *Locate the tumor thickness on the tumor thickness axis. Draw a line straight upward to the Points axis to determine the number of points received for tumor thickness. Repeat this process for the remaining axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate the sum on the Total Points axis. Draw a line straight down to find the 5-year cancer specific survival of the patient.*

Instructions to patient: *"Mr. X, if we had 100 men exactly like you, we would expect the predicted percentage from the nomogram to be free of disease specific death in 5 years, assuming no one died of another cause."*

Molecular factors

The tumor suppressor gene p53 is located on the short arm of chromosome 17 and has been implicated in the pathogenesis of many tumors. Mutations in this gene result in an anomalous protein with an extended half-life. The mutant protein accumulates in the nucleus of tumor cells and can be identified by immunohistochemical reaction. The role of p53 for predicting prognosis has been studied in different neoplasms. In 2002 Lopes et al. evaluated for the first time the prognostic significance of p53 in patients with SCC of the penis. They reported positive inguinal lymph nodes in 39.6% of p53 negative and 67.6% of p53 positive patients (p=0.01). In multivariate analysis p53 was an independent predictor of inguinal lymph node metastases (HR 4.8 – 95% CI 1.6 – 14.9). Overall 5- and 10-year survival rates in p53-negative patients were 64% and 54%, significantly higher than the 30% and 26% reported in p53 positive patients, respectively. Nevertheless, in multivariate analysis only patient age over 50 years and the presence of distant metastases were independent predictors of overall survival.[20] The results of this study were confirmed by Martins et al. in a series of 50 penile cancer patients. The p53 labeling index (LI) was reported to be 15 in patients with negative lymph nodes and 51.8 in those with inguinal metastases (p=0.02). Also in this study p53 was an independent predictive variable for lymph node involvement. Moreover, using a 10% cutoff, patients with <10% p53 had a significantly higher survival than those with >10% p53 (p=0.003).[67]

More recently Zhu et al. reported node metastases in 29% of patients with low p53 expression and in 67% of those with high p53 expression. Also in this study p53 was an independent predictor of node metastases, together with lymphatic and venous embolization.[68] The same authors observed

3-year cancer specific survival rates of 87% in patients with low p53 levels and 41% in those with high p53 (p<0.001) and p53 was reported to be an independent predictor of cancer-specific survival (p=0.01).[68]

Recently, Campos et al. studied the prognostic significance of E-cadherin and matrix metalloproteinases (MMP) 2 and 9.[41] E-cadherins are cell adhesion molecules whose decrease in expression is involved in the mechanism of metastasis.[69] Low E-cadherin immunoreactivity has been correlated with the risk of metastases in several neoplasms. MMP-2 and MMP-9 are part of a group of enzymes that degrade type IV collagen in the basal membrane and are involved in the invasion mechanism.[70]

Campos et al. reported lymph node metastases in 59.5% of patients with low E-cadherin expression and in 38.3% of patients with high E-cadherin levels (p=0.03). The stratification of lymph node metastases according to MMP-2 and MMP-9 levels did not show any significant difference. In multivariate analysis low E-cadherin levels were not independent predictors of survival. Campos et al. showed only clinical inguinal lymph node stage and lymphatic embolization as independent predictors of node involvement.[41]

In 2007 Zhu et al. reported 28% of patients with node metastases among those with high E-cadherin expression and 58% of patients among those with low E-cadherin levels (p=0.0009), but this variable was not an independent predictor of node involvement.[68]

Considering disease-free survival, Campos et al. identified high MMP-9 expression as an independent predictive factor (HR 3.2 – 95% CI 1.2 – 8.3), together with distant metastases (HR 57.9 – 95% CI 7.4 – 453.9) and urethral infiltration (HR 3.5 – 95% CI 1.3 – 9.2).[41] In contrast, Zhu et al. observed a significant difference in 3-year cancer-specific survival rates of patients with low and high MMP-9 (p=0.006), but this result was not confirmed in multivariate analysis.[68]

Ki-67 is a non-histone nuclear matrix protein expressed in all cell-cycle phases except G0. An assessment of Ki-67 protein expression by immunohistochemistry is a reliable means of evaluating tumor cell proliferation. In 2005, Berdjis et al. evaluated for the first time the prognostic significance of Ki-67 in patients with penile cancer. Although the mean Ki-67 labelling index (LI) was 51.4% in patients with and 38.6% in those without metastases, this difference did not reach statistical significance (p=0.07).[71] Zhu et al. reported inguinal metastases in 40% of patients with low Ki-67 expression and in 42% of those with high Ki-67 expression (p=0.861). The 3-year cancer-specific survival rates were 75% in patients with negative Ki-67 and 64% in those with positive Ki-67 (p=0.26).[68] In contrast, Guimaraes et al. observed a positive correlation between MIB-1/Ki-67 (>10%) and the presence of inguinal metastases.[42] Similar conclusions were drawn by Protzel et al. reporting lymph node metastases in none of patients with Ki-67 <15%, in 53% of those with Ki-67 between 15% and 60%, and in 100% of those with Ki-67 over 60% (p=0.005).[61]

Although extensively investigated in other tumors, proliferating cell nuclear antigen (PCNA) has been rarely evaluated in penile cancer. In 2000 Martins et al. found a possible association of the diffuse and strongly positive standard with lymph node metastasis risk.[72] However, there was no correlation with prognosis.[67]

More recently, Guimaraes et al. evaluated the prognostic meaning of PCNA in 125 patients with penile cancer. In this study node metastases were present in 31.7% of PCNA negative and 50% of PCNA positive patients. In multivariate analysis, PCNA was an independent predictive factor for node involvement (HR 2.94 – 95% CI 1.1 – 7.7), together with lymphatic and/or vascular embolization (HR 5.23 – 95% CI 1.9 – 13.7), lymph node clinical stage (HR 6.5 – 95% CI 2.2 – 16.2), and MIB-1/Ki-67 absence (HR 3.73 – 95% CI 1.4 – 9.7). However, PCNA was not an independent predictor of overall or disease-free survival.[42]

The cell membrane protein KAI11 ("Kang ai" = Chinese for "anti-cancer") also known as cluster of differentiation 82 (CD82) was originally described as a metastasis suppressor gene in prostate cancer.[73] This gene located on chromosome 11p11.2 is a member of the glycoprotein

transmembrane-4 superfamily. KAI11/CD82 plays a role in signal transduction, cell activation, development, proliferation and motility. Down-regulation of KAI11/CD82 is associated with metastatic progression and poor prognosis in several carcinomas.[74-76] Protzel et al. were the first researchers to evaluate the prognostic role of this protein in 30 penile SCC patients.[77] They observed a correlation between negative KAI11/CD82 and grading, and found that all patients with reduced or absent KAI11/CD82 expression had inguinal lymph node metastases (p=0.0002). Moreover, they reported a significant overall survival advantage in patients expressing more than 50% of these suppressor proteins.[77]

Genetic factors

In 2007 a study published by Poetsch et al. evaluated 62 microsatellite markers in 28 patients with penile cancer in order to identify markers able to predict metastatic progression of disease. Loss of heterozygosity (LOH) in more than 25% of primary tumors was found on six different chromosomes, including 2q, 6p, 8q, 9p, 12q and 17p13. Statistically significant correlations could be found between markers on chromosomes 6, 9 and 12 and tumor stage and metastasis.[78] These data deserve further evaluation in a more representative series.

Recommendations

1. The presence of metastases in regional lymph nodes is the main factor able to predict an unfavorable prognosis for patients with penile cancer (LE 3 - GR B).
2. The prognosis of patients with lymph node metastases may vary according to different variables, such as the number of positive lymph nodes, uni- or bilateral inguinal extension, pelvic node involvement, and the presence of lymph node capsular involvement (LE 3 - GR B).
3. The pathological and molecular features of the primary tumor may help to predict the risk of regional lymph node involvement in patients with penile cancer (LE 3 - GR B).
4. Histological subtype, pathological extension, histological grade, lymphatic and/or venous embolization, tumor thickness, and growth pattern are the most important variables of the primary tumor able to predict inguinal lymph node involvement. These parameters have to be included in the final pathological report of the penectomy specimen (LE 3 - GR B).
5. Nomograms are predictive models integrating prognostic information coming from the main clinical and/or pathological variables. The nomograms allow improvements in prognostic accuracy, compared to each single variable. Their use in clinical practice is potentially limited by the lack of external validation (LE 3 - GR B).
6. p53, E-cadherin, MMP-2, and MMP-9 are the most promising molecular prognostic factors to predict the risk of lymph node involvement in patients with penile cancer and their use in clinical practice awaits further confirmatory investigation (LE 3 - GR B).

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Société Internationale d'Urologie

The Société Internationale d'Urologie is the world's only truly international professional organization serving the global community of urologists. Founded in Paris in 1907, the SIU Central Office now serves its members from new premises in Montreal, Canada.

SIU members represent the full spectrum of clinicians and investigators from all subspecialties that come together to diagnose, treat and support patients with urological disease.

The Society's mission is to enable urologists in all nations, through international cooperation in education and research, to apply the highest standards of urological care to their patients.

The SIU promotes its mission objectives through biennial world congresses, training fellowships, the equipping and maintaining of centres in resource-constrained settings, provision of teaching materials and support of International Consultations on Urological Disease (ICUD).

Previous SIU/ICUD meetings have dealt with topics such Urogenital Trauma (2002), Bladder Cancer (2004), Congenital Genital Anomalies (2006), Stone Disease (2007) and Penile Cancer (2008). Consultations planned for the immediate future are Testicular Cancer (2009) and Urethral Stricture Disease (2010).

The Society has also recently launched a guest lecturer series in conjunction with national urological associations. Urology (the Gold Journal) is now the official journal of the Société Internationale d'Urologie.

Through its latest outreach activities and endorsement of regional urological meetings, the SIU continues to find new ways to further the art and science of urological care, worldwide.

Mission

The Society's mission is to enable urologists in all nations, through international cooperation in education and research, to apply the highest standards of urological care to their patients.

The main goals initially identified by the founders of the SIU are still valid today: to create and maintain the best possible conditions for communicating scientific information; to promote both formal and informal contacts between national urological societies; to foster cooperation between urologists from all parts of the world despite differences in material conditions, professional concerns and political views.

Concerning this last point, it particularly noteworthy that the SIU has continued to thrive in spite of major world conflicts. Indeed, members from nations at odds can meet at SIU Congresses to discuss professional topics in a spirit of collegiality, underscoring the successful international character of the Society.

Although there are many national and regional urological societies, the SIU is the only one truly international in scope and structure, attributes that the Society endeavours to maintain and develop.

Why Join the SIU?

The Société Internationale d'Urologie is an international democratic body whose first objective is to promote cooperation, education and exchange among urologists of all nations and cultures.

Joining the SIU raises funds for Society activities, heightens awareness of the important work that the Society undertakes in the interest of patient health and welfare, particularly in underserved countries, and provides the only truly international forum for specialists active in this area.

Application for membership must be supported by each country's National Section. Active members of each National Section elect a National Delegate and Deputy Delegate to liaise with the Society and to represent them at the National Delegates' Meeting held during each SIU World Congress.

All SIU members have a voice in this influential organization, which is committed to building increasingly far-reaching educational and endowment activities.

In addition, SIU members benefit from:

- Subscription to *Urology (*the *Gold Journal)*, which is published 12 times per year by Elsevier
- Reduced registration fee at SIU Congresses
- The regularly published SIU Membership Roster with complete listings of committees, national delegates, international members, bylaws, etc
- Peer recognition and membership in an internationally-recognized society.

Further information about the SIU can be found on its website at http://www/siu-urology.org/ or by contacting the SIU Central Office.

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