Journal of Clinical Trials and Case Studies

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Localized Penile Cancer Glans (Squamous Cell Carcinoma of Glans Penis Case Report)

Mohammed Abdul Qader Al-Malmi[1,*], Tawfeq Hassan Albadani[2]

[1,*] Assistant Professor of Dermatology and Venereology, Al-Kuwait University Hospital, Sana'a University Medical School, Sana'a, Republic of Yemen, Yemen

[2] Professor of Urology Sana'a Republic of Yemen, Yemen

CASE REPORT

ABSTRACT

Penile cancer is uncommon. Penile squamous cell carcinoma is the most common penile malignancy, behaves similarly to squamous cell carcinoma in other parts of the skin. Forty years old farmer Yemeni male patient presented with erosive ulcerative painful skin lesion in all his glans penis. The duration was one year. Skin biopsy showed. Most penile cancers are squamous cell carcinomas that demonstrate keratinization, epithelial pearl formation, and various degrees of mitotic activity. The normal rete pegs are disrupted, and invasive lesions penetrate the basement membrane and surrounding structures. No specific laboratory studies or tumor markers are diagnostic for penile cancer. The patient was treated by partial panectomy. There were no regional lymph node enlargements.

KEYWORDS

Penile cancer, Penile squamous cell carcinoma, Skin, Lymph node

Correspondence to: Dr. Mohammed Abdul Qader Al-Malmi, Assistant Professor of Dermatology and Venereology, Al-Kuwait University Hospital, Sana'a University Medical School, Sana'a, Republic of Yemen, Yemen, Email: maqma1952@gmail.com

Received: February 27, 2024, **Accepted**: March 15, 2024, **Published**: April 12, 2024

DOI: 10.1042/JCTCS.6.1.0013

Citation: Mohammed Abdul Qader Al-Malmi, 2024, Localized Penile Cancer Glans (Squamous Cell Carcinoma of Glans Penis Case Report)?. JCTCS. Vol 6.

CASE REPORT

Patients with carcinoma of the penis tend to delay seeking medical attention, with 15-50% delaying medical attention for more than 1 year from onset. This delay is attributed to embarrassment, guilt, fear, ignorance, and personal neglect. Patients often try to treat themselves with various skin creams and lotions. These may appear to be effective for a time, which further delays the diagnosis and worsens the prognosis. Delays may also attributable to the physician. Some patients with penile cancer report that they receive various salves and antibiotics from their primary care physicians before they see an urologist. A delay in diagnosis and therapy not only affects the likelihood of survival but also limits the ability to retain a functioning and cosmetically satisfactory result. Nearly 25% of dysplastic or neoplastic penile lesions are misdiagnosed as being benign. A biopsy should be considered in any uncircumcised male who presents with a penile lesion. These tend to originate on the glans penis and the undersurface of the prepuce. Many benign conditions may be found in this area, and only a biopsy can clarify the diagnosis. Surgery has been the traditional therapy for penile cancer.

Superficial penile carcinoma is typically managed with local resection, often with just a circumcision, whereas invasive disease is treated with partial or total penectomy and bilateral lymphadenectomy. Cancers on the glans or adjacent to the urethral meatus may be treated with Mohs surgery, in which a microscopic dissection can remove the cancer but obtain a good cosmetic result. Comparing treatment strategies is difficult because this is a rare cancer and no institution is able to amass enough experience to conduct clinical trials. Most published reports cover a span of a decade or longer. The single greatest predictor of disease-free survival is the presence of inguinal nodal metastasis. The morbidity associated with inguinal lymphadenectomy has discouraged surgeons from aggressively pursuing this treatment unless palpable nodes are present. There were more than 30% of patients without palpable inguinal nodes have micrometastatic disease. If these are removed, the surgery can be curative. In recent years, improved diagnostic techniques have been developed to determine the presence of lymph node metastases. Surgical techniques have been refined to reduce the morbidity

associated with penile and lymph node resection. Some surgeons are using laser treatment to remove small, superficial cancers. Radiotherapy is an alternative to conservative surgical treatment for stage T1-T2 tumors of the glans that are less than 4 cm in size.

Local chemotherapy with 5% 5-fluorouracil cream or 5% imiquimod cream have reported success rates of 70% and 52%. Systemic chemotherapy is recommended in patients with inguinal lymph node metastases. The results are poor in men with extensive metastases. Invasive penile cancer diagnosed in the absence of clinically evident nodal metastases (as determined by physical examination or imaging) can be treated with local resection and penile reconstruction. Inguinal lymph nodes need to be evaluated with bilateral lymphadenectomy or sentinel node biopsies. In some situations, radiation therapy to the penile tumor is applicable. Palpable inguinal lymph nodes should be assessed to determine the presence or absence of nodal metastasis. The 30% incidence of micrometastases in nonpalpable inguinal lymph nodes emphasizes the importance of nodal assessment. The ability to identify a sentinel node has been a valuable adjunct in the refinement of surgical management. Various imaging techniques have shown increasing sensitivity for identifying these nodes, sparing the need for extensive, bilateral inguinal lymphadenectomy, which is associated with a high degree of morbidity. In the past, an excisional margin of 2 cm around the cancer was thought to be necessary, but with improved histopathology techniques, a margin of 0.5-1 cm may be sufficient. In addition, although a 4-week to 6-week waiting period was once believed to be necessary to treat the patient with antibiotics prior to surgery. This would allow lymph nodes that were enlarged as a result of infection to return to their normal state. Currently, tumor excision and lymph node excision are performed at the same time. The presence of palpable inguinal nodal metastasis is managed by a bilateral radical lymphadenectomy followed by an extensive pelvic lymphadenectomy. Postoperative chemotherapy and radiation therapy is used depending on the surgical outcome. Penile tumors can originate anywhere on the penis, but most are found on the glans (48%) and prepuce (21%). The presentation can be a hyperemic area on the glans or near the urethral meatus. The cancers can range from an area of subtle induration to a small excrescence or papule. They can be exophytic or flat, or an ulcerated lesion may be present. (Figure 1) Sensations of itching or burning under the foreskin or an ulceration of the glans are the most common presenting symptoms. Pain is rarely present. A circumcised male rarely develops penile cancer; however, men with chronic lymphocytic leukemia are predisposed to the development of squamous cell carcinomas that can occur anywhere on the body, including the penis. Tumors may initially form on the corona of the glans and spread superficially across the glans and into the prepuce. Phimosis may conceal the cancer, allowing it to progress.

Eventually, as the cancer grows, erosion through the prepuce, a foul odor, and a discharge are evident. Buck fascia acts as a natural barrier to the corpora, but over time, the cancer invades the corpora. As these cancers spread over the glans, they may involve the urethral meatus and grow into the urethra. The etiology of these cancers may be related to chronic exposure to carcinogens contained in smegma that collects within the prepuce although no specific carcinogens have been identified. Patients who are diagnosed with penile cancer have various treatment options. If the tumor is smaller than 2 cm (and particularly if it is confined to the prepuce), circumcision may be all that is necessary. Penile cancer tends to remain confined to the skin for long periods, often years, but when it invades the deeper tissues, the cancer has ready access to lymphatics and blood vessels and the growth rate is rapid. Penile cancer is rare in Western countries. According to the American Cancer Society annual statistics for 2010, 1250 penile cancers were diagnosed in the United States, and 310 deaths were reported (24.8%). This high death rate underscores the seriousness of this cancer. For comparison, only 3% of men with prostate cancer die from this disease. Penile cancer accounts for 0.4-0.6% of all malignancies in the United States and Europe. In the rest of the world, the situation is different and represents an important health problem. Penile carcinoma represents 20-30% of all cancers diagnosed in men who live in Asia, Africa, and South America. In urban India, the age-adjusted incidence of penile cancer ranges from 0.7-2.3 cases per 100,000 men. In rural India, the rate of penile cancer is 3 cases per 100,000 men, accounting for more than 6% of all malignancies in this population. In underdeveloped countries such as Uganda, the incidence is 2.8/100,000 and 1% of the men have developed this cancer by age 75. In Brazil, the age-adjusted incidence of penile cancer is 8.3 cases per 100,000 populations.

Barnholtz-Sloan et al studied the incidence trends of primary penile cancer in the United States using data from The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database of 1,817 men. They found that the overall incidence of primary malignant penile cancer has been decreasing over the past 3 decades. The overall incidence was 0.84 per 100,000 from 1973-1982, 0.69 from 1982-1992, and 0.58 from 1993-2002. Most of the cancers were squamous cell and originated on the glans. From 1993-2002, the incidence was highest among Hispanics (1.01 per 100,000), followed by Alaskan Native Americans (0.77 per 100,000) and African Americans (0.62 per 100,000). Penile cancer is rare in circumcised men, particularly if they were circumcised as a neonate. Seyam et al studied penile carcinoma in 22 men who had been circumcised. Eighteen of these patients came from the southwest part of Saudi Arabia and had undergone late ritual circumcision. This practice, known as "Tihamah" circumcision, involves removing an extensive amount of skin, including some of the pubic skin. This procedure results in extensive cicatrization, which is probably the underlying cause of the resulting squamous cell cancer. Radiation therapy was attempted in a few of the patients, with unsuccessful results, whereas the group treated with surgery had a median survival of 34 months. Penile cancer tends to be a disease of older men. The incidence of penile cancer increases abruptly in men aged 60 years or older and peaks in men aged 80 years. However, the tumor is not unusual in younger men. One study

reported that 22% of patients with penile cancer were younger than 40 years, and 7% were younger than 30 years. The frequency of penile carcinoma varies according to hygienic practices and cultural and religious beliefs.

Phimosis is present in at least 25-75% of men with this disease. Information on presence of phimosis often goes unrecorded in underdeveloped countries, and epidemiologic data are lacking. Circumcision has been well established as an effective prophylactic measure for penile cancer. Data from most large series have demonstrated that penile cancer is almost never observed in individuals who are circumcised in the neonatal period. The disease is found more frequently when circumcision is delayed until puberty. Adult circumcision offers little or no protection. No firm evidence indicates that smegma acts as a carcinogen, although this belief is widely held. The role of viral infection continues to be studied. Both penile cancer in men and cervical cancer in women have been associated with human papillomavirus (HPV) infection. In women whose sexual partners had penile cancer, the prevalence of cervical cancer is increased 3- to 8-fold. HPV-16 and HPV-18 have been found in one third of men with penile cancer. Whether these viruses are involved with causation of the cancer or are found as saprophytes has not been determined. No data have indicated that herpes viral infections cause penile cancer. Madsen et al studied a population that included 71 patients with invasive or in situ squamous cell carcinoma, 86 prostate cancer controls, and 103 men as population controls. PCR was used to examine for HPV in tissue samples of 37 patients with squamous cell carcinoma. The study found high-risk HPV in 65% of the 37 patients, of whom 22 of 24 (92%) were found to have HPV-16. Risk factors included early and high sexual activity, the lifetime number of sexual partners, the number of sexual partners prior to age 20 years, age at first occurrence of intercourse, penile-oral sex, a history of anogenital warts, and never having used condoms. A history of phimosis and priapism occurring more than 5 years prior to diagnosis were also significant risk factors. Cigarette smoking and chewing tobacco is also considered to be a risk factors. Harish and Ravi reported that the risk for those smoking more than 10 cigarettes a day was 2.14.

The combination of chewing tobacco and cigarette smoking raised the risk to 3.39. Maden et al found that the risk of penile cancer in men who were smoking at the time of diagnosis was 2.8 times that of men who never smoked. Penile trauma, usually consisting of small tears or abrasions involving the prepuce, and a history of chronic balanitis that occurred more than 2 years prior to diagnosis had an odds ratio of 23 for carcinoma in situ and 4.6 for invasive cancer. Hellberg et al reported that multiple episodes of balanitis had a relative risk of 9.49. These observations support the theory correlating chronic inflammation to the development of cancer. Abnormalities considered to be nonmalignant include cutaneous horns, pseudoepitheliomatous keratotic and micaceous balanitis, balanitis xerotica obliterans, giant condyloma, and bowenoid papulosis. Penile intraepithelial neoplasia is considered to be premalignant, but only 5-15% of these lesions evolve into invasive squamous cell carcinoma. When carcinoma in situ (CIS) occurs on the glans, it is termed erythroplasia of Queyrat; however, when it occurs on the follicle-bearing skin of the shaft, it is termed Bowen disease. CIS can also develop in the tissue around the urethral meatus and spread down the urethra.

These lesions have a red to red-brown appearance and generally have an irregular border. Suspicious lesions should prompt a biopsy to establish a diagnosis. The National Cancer Institute's SEER program was used to gather data on 1605 men diagnosed with squamous cell carcinoma of the penis. CIS was diagnosed in 37% of this population, localized disease was diagnosed in 39%, regional disease was present in 13%, distant disease was present in 2.3%, and unstaged disease remained in 7.9%. According to SEER data, the proportion of men presenting annually with CIS has tended to increase, although the number of men with localized disease has decreased. Older age at diagnosis was associated with a higher stage of disease. The mean time until death from cancer was 66.6 months in those with CIS, 50.1 months in those with localized disease, 32.4 months in those with regional disease, and 7.4 months in those with distant metastases. Overall, 22.4% of the patients in this database died of this cancer.

Penile cancers usually begin as small lesions on the glans or prepuce. They range from white-grey, irregular exophytic to reddish flat and ulcerated endophytic masses. They gradually grow laterally along the surface and can cover the entire glans and prepuce before invading the corpora and shaft of the penis. The more extensive the lesion, is the greater the possibility of local invasion and nodal metastasis. Penile cancers may be papillary and exophytic or flat and ulcerative. Untreated, penile autoamputation can occur. The growth rates of the papillary and ulcerative lesions are similar, but the flat ulcerative lesions tend to metastasize to the lymph nodes earlier and are therefore associated with a lower 5-year survival rate. Cancers larger than 5 cm and those involving more than 75% of the shaft are associated with a high prevalence of nodal metastases and a lower survival rate, but a consistent relationship among the size of the cancer, the presence of inguinal node metastases, and survival has not been identified.

The Buck fascia, which surrounds the corpora, acts as a temporary barrier. Eventually, the cancer penetrates the Buck fascia and the tunica albuginea, where the cancer has access to the vasculature and from which systemic spread is possible. Metastasis to the femoral and inguinal lymph nodes is the earliest path for tumor dissemination. The lymphatics of the prepuce join with those from the shaft. These drain into the superficial inguinal nodes. Because of lymphatic crossover, cancer cells have access to lymph nodes in both inguinal areas. The lymphatics of the glans follow a different path and join those draining the corpora. A circular band of lymphatics that drains to the superficial nodes is located at the base of the penis and can extend to

both the superficial and deep pelvic lymph nodes. The superficial inguinal nodes drain to the deep inguinal nodes, which are beneath the fascia lata. From here, drainage is to the pelvic nodes.

Multiple cross connections exist at all levels, permitting bilateral penile lymphatic drainage. Untreated metastatic enlargement of the regional nodes leads to skin necrosis, chronic infection, and, eventually, death from sepsis or hemorrhage secondary to erosion into the femoral vessels. Clinically apparent distant metastases to the lung, liver, bone, or brain are unusual until late in the disease course, often after the primary disease has been treated. Distant metastases are usually associated with regional node involvement. Microscopically, the tumors vary from well-differentiated keratinizing tumors to solid anaplastic carcinomas with scant keratinization. Most tumors are highly keratinized and are of moderate differentiation. Poorly differentiated carcinomas have variable amounts of spindle cell, giant cell, solid, acantholytic, clear cell, small cell, warty, basaloid, or glandular components.

Penile carcinoma follows a relentless and progressive course that proves to be fatal in most untreated patients within 2 years. The typical SCC has a recurrence rate of 28% and lymph node metastases are found in 28-39% depending upon the extent and grade of the tumor. The mortality rate is 20-38% with a 10-year survival rate of 78%. Spontaneous remission has not been reported. Typical presentations of penile cancer include a lesion that has failed to heal, a subtle induration in the skin, a small excrescence, a papule, a pustule, a warty growth, a large exophytic growth, or a reddened area on the glans. The malignancy may appear as shallow erosion or a deep ulceration with rolled edges. Because most of patients with penile cancer are uncircumcised, they may have a phimosis that obscures the tumor and allows it to grow undetected. Many men do not seek medical attention until the cancer has eroded through the prepuce and has become malodorous because of infection and necrosis. In rare cases, an inguinal mass ulcerates, suppurates, or hemorrhages. Few symptoms are associated with the development of penile cancer. Even after significant local tissue destruction, pain is uncommon. Patients with advanced metastatic cancer may report weakness, weight loss, and fatigue; the penile lesion may bleed. The presence of a nonhealing penile lesion usually prompts the patient to visit a physician. While carcinoma may manifest as a hyperemic patch on the glans that is characteristic of erythroplasia of Queyrat or as an ulcerated growth on the inner surface of the prepuce, the differential diagnoses include benign and premalignant lesions. Penile lesions can be categorized as benign, premalignant, or malignant neoplasms. Benign lesions include pearly penile papules, hirsute papillomas, and coronal papillae.

These lesions do not require treatment and are usually found on the glans in uncircumcised males. Rashes, ulcerations from irritation, and allergic reactions or infections must be considered. Some histologically benign lesions are potentially malignant (premalignant) or have been associated with the presence of squamous cell carcinoma. The most common is balanitis xerotica obliterans. This is a variation of lichen sclerosus ET atrophicus and manifests as a white patch on the prepuce or glans, where it usually involves the urethral meatus. This can produce severe cicatrization, leading to obstruction of the urethra. Leukoplakia manifests as solitary plaque or multiple whitish plaques, which often involve the meatus. Leukoplakia has been associated with squamous cell carcinoma. Viral lesions include condyloma acuminata, which are soft papillomatous growths. They are known as venereal warts and have a predilection for the genital and perineal regions. These lesions are usually sexually transmitted and are caused by HPV. Viral types 6, 11, 42, and 44 are associated with low-grade dysplasia.

Types 16, 18, 31, 33, 35, and 39 are associated with neoplastic changes. De Paula et al studied the presence of koilocytosis, which is a feature of productive HPV infection and is characterized by large halos around cell nuclei. Koilocytosis is found in approximately 30%-60% of patients with penile cancer. They found that the presence of koilocytosis correlated with Jackson stage and grade but not with nodal disease or survival. Lichen sclerosis, also known as balanitis xerotica obliterans, is a chronic lymphocyte-mediated skin disease that can develop on any cutaneous surface and has been associated with squamous cell carcinoma of the penis. Biopsy of the lesion should be obtained prior to initiating therapy. A direct causative link between these entities has not been established, but the presence of a chronic inflammatory lesion is thought to promote the development of many types of cancers. A study by Mannweiler et al revealed HPV-negative carcinomas were correlated with advanced lichen sclerosus and lichen planus, differentiated penile intraepithelial neoplasia, and accumulation of T lymphocytes with monoclonal rearrangement of the T-cell receptor γ locus. Kaposi sarcoma manifests as a cutaneous neovascular lesion that is raised, usually painful, and often ulcerated with a bluish discoloration.

Patients with AIDS are predisposed to develop this condition. Giant condyloma acuminata or a Buschke-Löwenstein tumor differs from the standard condyloma in that it displaces, invades, and destroys adjacent structures by compression, whereas the standard condyloma remains superficial and never invades. Despite their large size and invasive potential, Buschke-Löwenstein tumors show no signs of malignant change upon histologic examination. Malignant carcinomas include variants of squamous cell carcinoma such as CIS, erythroplasia of Queyrat, or Bowen disease. The diagnosis depends on their appearance and the site of origin. Erythroplasia involves the glans, prepuce, or penile shaft, while similar lesions on the remainder of the genitalia

and perineum are termed Bowen disease. Regardless of the terminology and clinical presentation, these are carcinomas with the same malignant potential; biopsies should be performed, and the carcinoma should be staged and treated.

Herpes viral infections have not been associated with the development of penile cancers. Indications for therapy and therapeutic options depend on the histologic diagnosis of cancer established based on biopsy findings, the location and size of the tumor, and the presence or absence of palpable inguinal lymphadenopathy. All patients with penile cancer require therapy because spontaneous regression does not occur and, untreated, the cancer ultimately causes death. Rippentrop et al studied the surgical therapy status among the 1605 men identified in the SEER database. Surgical therapy was recorded in 1422 patients, of whom 721 (50.7%) underwent some form of surgery. Excisional biopsy was performed in 19.7%, and topical therapy with laser or cryoablation was used in 0.3%. Of those undergoing surgery, 13.1% underwent partial penectomy without lymphadenectomy, 2.1% underwent a combined procedure, and only 0.5% required radical penectomy.

The anatomy of the penis has important implications for the diagnosis and treatment of penile cancer. Embryologically, the 3 erectile bodies of the penis arise from the paired genital tubercles, which give rise to the corpora cavernosa, the caudal portion of the urogenital sinus that creates the corpora spongiosum, and the paired urethral folds, which join in the midline. For purposes of description, the penis may be divided into the root, which is located within the superficial perineal pouch and is the primary fixation point; the body, which contains the 3 corpora and the overlying tissues; and the glans, which sits as a cap on the corpora cavernosa but is a part of the corpora spongiosa. The superficial fascia is continuous with dartos fascia posteriorly and with the Scarpa and Camper fascia anteriorly. The superficial fascia consists of a single layer with loose connections to the overlying skin. The corpora are covered by a layer of dense fibrous tissue called the tunica albuginea. The corpora cavernosa are incompletely separated by the septum penis, a thin layer of fibrous tissue continuous with the tunica albuginea. The fascia overlying the corpora cavernosa blends with the fascia of the urogenital diaphragm. The erectile tissue within the corpora is composed of a spongelike network of endothelium-lined sinusoidal spaces. No specific laboratory studies or tumor markers are diagnostic for penile cancer.

A general evaluation, which includes a CBC count; a chemistry panel with liver function tests; and an assessment of cardiac, pulmonary, and renal status, is helpful as a baseline and in the detection of any unsuspected problems. Patients with advanced penile cancer may be anemic, with leukocytosis and hypoalbuminemia. Hypercalcemia has been found in some patients in the absence of metastases. MRI and ultrasonography are useful for local cancer staging and for assessing the inguinal lymph nodes. These studies may be helpful for detecting tumor invasion into the corpora. MRI produces sharp images of the penile structures, is accurate for demonstrating invasion of the corpora, and can help the physician determine the extent of the cancer along the surface of the penis in patients with tumors larger than 2 cm. Both MRI and CT scanning can demonstrate enlarged pelvic and retroperitoneal lymph nodes. Positron emission tomography (PET) and CT scanning have not been studied extensively but may be helpful and should be obtained in patients with high-grade and extensive local disease and in those with evidence of inguinal node involvement. CT images in men with proven unilateral or bilateral cancer with central node necrosis and/or irregular nodal borders of the regional nodes are very useful to identify high-risk patients. Graafland et al demonstrated an association between these unfavorable pathologic features and poor prognosis, with a sensitivity of 95%, a specificity of 82% and a diagnostic accuracy of 87%. Rarely, chest radiography can help detect metastases. However, the preferred study to evaluate for metastases is CT scanning. A technique to identify lymph node metastases using MRI following the intravenous injection of ferromagnetic particles has shown a high degree of sensitivity. Tabatabaei et al studied 7 patients with this imaging and found a sensitivity of 100%, a specificity of 97% and a positive predictive value of 81.2% in the ability to detect micrometastatic disease.

Further study are necessary to determine the tumor burden needed for this imaging modality to be effective, but current results indicate that it is more accurate than conventional CT scanning. PET/CT imaging using 18F-FDG was used to study 42 patients with nonpalpable inguinal nodes. Five of these patients had micrometastatic disease but the PET/CT found tumor in only one patient. Another study using 18F-FDG-PET/CT scan imaging conducted by Schlenke r et al on 35 patients with invasive penile carcinoma found that integrating PET/CT scanning into preoperative procedures could avoid surgical staging in selected patients. The most important diagnostic test is a biopsy. This may be an excisional biopsy if the cancer is small or the lesion is confined to the prepuce and a circumcision is acceptable. The biopsy should contain tissue beneath the tumor, if this is feasible, in order to help stage the disease. (Figure 2-4). CT-guided or ultrasound-guided fine-needle aspiration of enlarged lymph nodes may aid the urologist in planning therapy. Aspiration biopsies of sentinel nodes using the identification techniques described below have also been reported. Kroon et al reported that only 9 of 23 patients (39%) were detected with fine-needle aspiration biopsy. Sentinel node biopsy may be of assistance in determining the need for extensive inguinal lymphadenectomy. Various methods have been used to identify the sentinel node. One method involves intradermal injection of 2 mL of patent blue dye around the tumor. Approximately 15 minutes later, the node can be identified and removed for histologic assessment. Lymphoscintigraphy is another method used to identify the sentinel node. This technique, developed at The Netherlands Cancer Center Institute,

involves injecting technetium-99m nanocolloid around the primary tumor. Following the injection, dynamic images are taken with a gamma camera to visualize lymphatic drainage. Static scintigrams are obtained 2 hours after the injection.

A hot spot in the inguinal area is considered to be a sentinel node, and its position is marked on the skin. In some instances, both techniques are used to identify the sentinel node. Kroon et al found that that the size of the metastasis was predictive of nonsentinel node metastasis. They reported that, in groins with only micrometastases in the sentinel node, none of the other nodes were involved. Tabatabaei and McDougal reported on their results using lymphotrophic nanoparticle-enhanced MRI and found that this technique yielded 100% sensitivity and 97% specificity. The major limitation of these techniques is the need to perform the test in all patients regardless of the presence of clinically normal nodes and histologic features of the primary tumor. Another possible concern is thrombosis of the lymphatic vessels cause by inflammation. Finally, inexperience with these techniques is an obstacle. It has been estimated that experience with 25 patients is needed to achieve the 4.8% false-negative rate reached by the Netherlands group, and few centers see enough patients to become proficient. Most penile cancers are squamous cell carcinomas that demonstrate keratinization, epithelial pearl formation, and various degrees of mitotic activity. The normal rete pegs are disrupted, and invasive lesions penetrate the basement membrane and surrounding structures. (Figure 2-4). Erythroplasia of Queyrat, a red, velvety, well-marginated lesion usually occurring on the glans, is characterized by atypical hyperplastic cells that appear disoriented and vacuolated and have hyperchromatic nuclei and multiple mitotic figures. The submucosa shows capillary proliferation and ectasia with a surrounding inflammatory infiltrate rich in plasma cells. Campos et al studied E-cadherin (cell adhesion molecules involved in the metastatic process), matrix metalloproteinase (MMP)–2, and MMP-9 (part of a group of enzymes that degrade collagen type IV in the basement membrane). In the 125 available tumor specimens and clinical records, they found that low levels of E-cadherin and high expression of MMP-9 represented independent risk factors for nodal disease. Guimaraes et al examined the value of proliferating cell nuclear antigen (PCNA) and MIB-1/Ki-67 to determine if these might serve as prognostic factors in predicting nodal metastasis. PCNA was an independent factor in univariate and multivariate analysis (RR, 2.94; 95% confidence interval, 1.1-7.7).

Unexpectedly, a high expression of MIB-1/Ki-67 reactivity correlated with a decreased incidence of nodal metastases. Although these markers did have predictive value, they added little to the predictive value of tumor stage and grade and the presence of vascular invasion. Stankiewicz et al found thatKi-67 was only a moderate surrogate marker for HPV infection in patients with penile squamous cell carcinoma. Ki-67 did not show prognostic value for cancer-specific survival or overall survival. No universal staging system has been established for penile cancer. A detailed and accurate assessment of the primary tumor, including identification of regional and distant metastatic disease, is important for selecting appropriate therapy and for assessing and communicating results. The Jackson and TNM systems are used, although the TNM system is preferable. In the Jackson system, characteristics of the primary lesion, such as size and confinement to the epidermis (superficial or invasive), are not used. The presence and extent of nodal metastases is not addressed. Histologic criteria are not used, even though the grade and extent of invasion is important. Solsona et al presented the European Association of Urology (EAU) guidelines on penile cancer. They proposed 3 risk groups for patients with clinically negative or occult nodal metastases: low risk, stage T1, grade 1; intermediate, stage T1, grade 2 or 3; and high, T2-T3, and grade 2-3. Most patients with positive sentinel node biopsy findings tend to fall into the high-risk category. Most penile cancers are low grade, but correlation between grade and survival is lacking. High-grade disease is associated with regional lymph node metastases. The strongest predictor for survival is the presence or absence of nodal metastases. The optimum surgical margin has been reduced from the classical 2 cm to 1 cm or, in some instances, to 0.5 cm, without any adverse consequences related to cancer recurrence or survival. The advantage of a smaller margin is important because nearly 80% of penile squamous cell carcinomas are distal, presenting on the prepuce, glans, or in the coronal sulcus. These lesions can be managed with local excision and reconstruction.

The Jackson classification is as follows:

- Stage I (A): The tumor is confined to the glans, prepuce, or both.
- Stage II (B): The tumor extends onto the shaft of the penis.
- Stage III (C): The tumor has inguinal metastasis that is operable.
- Stage IV (D): The tumor involves adjacent structures and is associated with inoperable inguinal metastasis or distant metastasis.

The TNM classification of the primary tumor (T) is below. Note that the following description is devoid of N (node) and M (metastasis) descriptions. These stages simply relate the presence or absence of nodal and distant metastases.

- TX: Primary tumor cannot be assessed.
- T0: Primary tumor is not evident.

- Tis: CIS is present.
- Ta: Noninvasive verrucous carcinoma is present.
- T1: Tumor invades subepithelial connective tissue.
- T2: Tumor invades corpora spongiosum or cavernosum.
- T3: Tumor invades the urethra or prostate.
- T4: Tumor invades other adjacent structures.

The WHO histopathological classification is as follows:

- Grade 1 - Well differentiated, with 33% undifferentiated cells
- Grade 2 - Moderately differentiated, with 33%-66% undifferentiated cells
- Grade 3 - Poorly differentiated, with more than 66% undifferentiated cells

Novara and colleagues from the GUONE Penile Cancer Project compared the prognostic accuracy of the Solsona and European Association of Urology (EAU) risk groups in predicting lymph node metastases. They studied clinical and pathology data from 175 patients with squamous cell carcinoma from 1980-2002. Both groups used variations of the pathologic features and primary tumor stage. Although both risk groups could predict the probability of nodal metastases, their prognostic accuracy was poor when the data were analyzed according to the ROC curve analysis. There was no medical therapy in this case patient. He treated by partial pnectomy. Follow-up in patients with penile cancer is necessary to evaluate healing following the use of medicines applied to the tumor and following surgery, laser therapy, or radiation therapy. The frequency of follow-up visits depends on the therapy, but long-term observation is necessary to detect any areas of tumor recurrence. The patient was healthy and deal with sexual interdourse very good. No surgical complications are associated with excision of the tumor by partial penectomy. The prognosis in this case patient was very good.

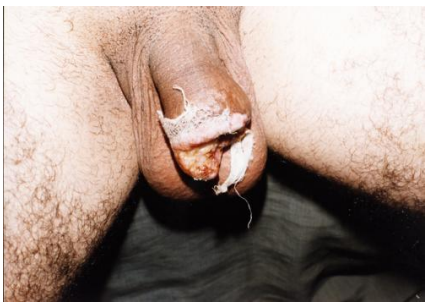

Figure 1: Localized erosive ulcerative skin lesion in the glans penis.

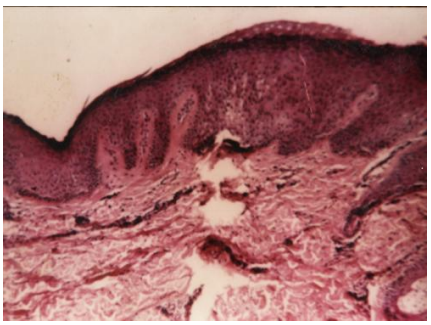

Figure 2: Keratinization, epithelial pearl formation, and various degrees of mitotic activity. The normal rete pegs are disrupted, and invasive lesions penetrate the basement membrane and surrounding structures.

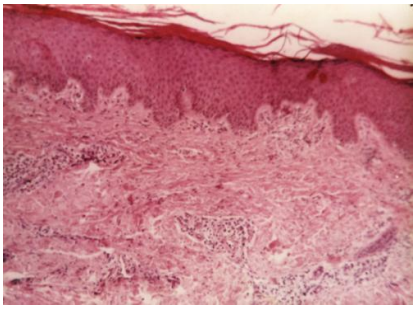

Figure 3: Keratinization, epithelial pearl formation, and various degrees of mitotic activity. The normal rete pegs are disrupted, and invasive lesions penetrate the basement membrane and surrounding structures.

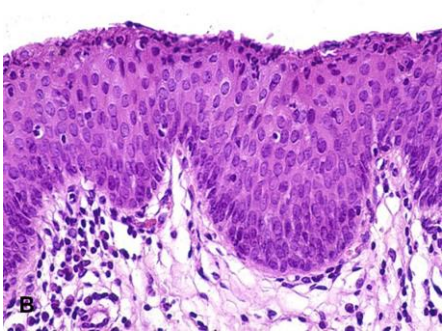

Figure 4: Keratinization, epithelial pearl formation, and various degrees of mitotic activity. The normal rete pegs are disrupted, and invasive lesions penetrate the basement membrane and surrounding structures.

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