

# Chapter 48

## Penile Cancer

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### 48.1 Epidemiology

Penile cancer is a rare malignant disease and an estimated 1,100 new cases will be diagnosed each year. The annual incidence is estimated to be 1 in 100,000 males, accounting for less than 1 % of all cancers in men [1]. The higher incidence is presented in some areas of South America, Africa, and Asia. The male circumcision seems to be very effective in preventing the development of penile neoplasm [2]. Chronic irritation of the penis from the smegma and urethritis especially when phimosis is coexisting is believed to be the main causative factor of penile cancer. Also, the development of penile cancer has been associated with certain subtypes (in 16 and 18) of the Human Papillomavirus [3, 4].

### 48.2 Pathology

#### 48.2.1 *Pre-malignant Dermatological Lesions*

Leukoplakia, sclerotic balanitis and giant warts associated with HPV (Buschke-Löwenstein tumors) are classified in this category.

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### **48.2.2 *In Situ Carcinoma of the Penis***

Erythroplakia of Queyrat and Bowen disease are included here.

### **48.2.3 *Infiltrating Penile Carcinoma***

Histologically it consists of squamous cells in 95 % of the cases, while the remaining 5 % can consist of several histologic types, such as sarcoma, melanoma, and rarely basal cell carcinoma to be the most frequent.

## **48.3 Natural History: Clinical Presentation**

The clinical signs in penile cancer vary from a small and usually painless skin damage (ulcerative or exophytic) to extensive damage that can automatically lead to partial amputation of the penis (Fig. 48.1). The predominant sites of the primary lesion are the following: glans penis, prepuce, coronal sulcus and body of penis. The clinical examination should include consideration of the following tumor characteristics: (1) Diameter, (2) Localization, (3) Presence of ulceration, (4) Number of ulcerations, (5) Color, (6) Margins – Mobility of the lesion.

Several patients suffered from phimosis for a long time, while others are complaining of phimosis developed in a short time and this clue should lead us to suspect that penile cancer can be hidden. The patient experiences fear and embarrassment, which probably contributes to delayed diagnosis. Other symptoms may include itching, burning, groin mass and bleeding, and while in those cases where the mass is located close to the external urethral opening, urinary and obstructive symptoms may be present.

The absence of pain in the early stages represents the main reason that explains why patients delay to refer to a physician. In most cases, carcinoma of the penis is characterized by slow locoregional progression. If untreated, it usually grows slowly leading to infiltration of the glans, corpora cavernosa, corpus spongiosum. Finally major bleeding, fistulas, and even urine retention may occur.

The inguinal lymph nodes are the most common site of metastatic spread. The prepuce and the skin of the penis drain to the superficial inguinal lymph nodes, while the glans and the corpora cavernosa to the deep inguinal lymph nodes. Usually, tumours progress slowly at primary and regional sites rather than spread to distant areas. Tumours of the penile urethra spread firstly to the inguinal lymph nodes, whereas those of the bulbomembranous and prostatic urethra metastasize to the pelvic lymph nodes. Approximately one-third of men will present with either clinically or pathologically involved lymph nodes. In 50 % of the cases, enlargement of the lymph nodes is often related to inflammatory or infectious processes.

**Fig. 48.1** Penile cancer

Conversely, between 20 % and 40 % of patients with clinically negative inguinal lymph nodes have occult metastases [1]. Distant, hematogenous spread is uncommon even in patients with advanced locoregional disease, and usually occurs in the lungs, liver and bones.

#### 48.4 Diagnostic Workup

The diagnosis should be confirmed with biopsy of the primary neoplasm. The cytological examination of lymph nodes after fine needle aspiration helps in the differential diagnosis between metastatic and inflammatory lesion [5]. Differential diagnosis should include venereal disease, urethral stricture, urethral trauma, and urethral polyps. Computed tomography and magnetic resonance imaging is useful in the identification of enlarged pelvic lymph nodes in patients with involved groin lymph nodes. Limited prospective data regarding the use of positron emission tomography with CT are available [6, 7].

## 48.5 Staging

The American Joint Committee on Cancer (AJCC) staging system for carcinoma of the penis 7th Edition (2010) is as follow:

<i>Primary Tumor (T)</i>	
<b>Tx</b>	Primary tumor cannot be assessed
<b>T0</b>	No evidence of primary tumor
<b>Tis</b>	Carcinoma in situ (Bowen's disease, Queyrat's erythroplakia)
<b>Ta</b>	Noninvasive verrucous carcinoma
<b>T1a</b>	Tumor invades sub epithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3–4)
<b>T1b</b>	Tumor invades sub epithelial connective tissue with lymph vascular invasion or is poorly differentiated
<b>T2</b>	Tumor invades corpus spongiosum or cavernosum
<b>T3</b>	Tumor invades urethra
<b>T4</b>	Tumor invades other adjacent structures (perineum, pubic symphysis)
<i>Regional Lymph Nodes (N)</i>	
<b>cNx</b>	Regional lymph nodes cannot be assessed
<b>cN0</b>	No palpable or visibly enlarged inguinal lymph nodes
<b>cN1</b>	Palpable mobile unilateral lymph node
<b>cN2</b>	Palpable mobile multiple or bilateral inguinal lymph nodes
<b>cN3</b>	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral
<b>pNx</b>	Regional lymph nodes cannot be assessed
<b>pN0</b>	No regional lymph node metastasis
<b>pN1</b>	Metastasis in a single inguinal lymph node
<b>pN2</b>	Metastasis in multiple or bilateral inguinal lymph nodes
<b>pN3</b>	Extra nodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral
<i>Distant Metastasis (M)</i>	
<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis (includes lymph node metastasis outside the true pelvis)

### 48.5.1 Stage/Prognostic Groups

**0:** Tis N0 M0

Ta N0 M0

**I:** T1a N0 M0

**II:** T1b N0 M0

T2 N0 M0

T3 N0 M0

**IIIa:** T1-3 N1 M0

**IIIb:** T1-3 N2 M0

**IV:** T4 Any N M0

Any T N3 M0

Any T Any N M1

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## 48.6 Prognostic Factors

The main prognostic factors are the extension of the primary tumor and lymph nodal status. The probability of nodal involvement is related to the size, location, and grade of the primary. Invasion of deep-seated structures such as corpora cavernosa is associated with a higher risk of deep inguinal node involvement. Pelvic lymph node involvement is related to a worse prognosis [8].

## 48.7 Treatment

### 48.7.1 Local Therapy

Treatment for carcinoma in situ and very small tumors includes topical imiquimod and 5 fluorouracil (5-FU). For larger neoplasms, conservative laser surgery or Mohs micrographic surgery can be used.

### 48.7.2 Surgery

Surgical treatment for small tumors may be local excision, such as circumcision or laser therapy. In advanced tumors, operations like penectomy, orchiectomy, scroterectomy, or cystoprostatectomy are used indicated. Lesions limited to the prepuce may be managed with circumcision. Lesions on the glans are usually treated by partial penectomy. Larger can be treated by partial or total penectomy. If surgical margins of 2 cm can be achieved, partial penectomy is the procedure of choice. If a clear margin cannot be achieved, total penectomy is warranted [9, 10].

### **48.7.2.1 Surgical Treatment of Inguinal Lymph Nodes**

The morbidity of radical lymphadenectomy and the relative small probability of pathologic involvement of groin nodes have resulted in surveillance as the initial management of regional lymph nodes in clinically negative cases at some centres [11, 12]. Lymph node dissection is associated with complications like wound dehiscence, infection, lymphocele, chronic lymphedema, or venous thromboembolism. Sentinel node biopsy represents as a less morbid method of evaluating inguinal nodes [13]. An extended pelvic nodal dissection is justified in patients with evidence of inguinal involvement (positive biopsy of Cloquet's node) that they may be at risk for microscopic metastases. Patients with clinically negative lymph nodes (stage I disease and well-differentiated histology) may benefit from elective irradiation to the inguinal lymph nodes.

### **48.7.3 Chemotherapy**

The cornerstone of chemotherapy combinations for advanced penile cancer is cisplatin. There are trials with cisplatin-based combinations that showed response rates of 15–55 % and overall survival of 5–12 months [14, 15]. The chemotherapy combinations that have been studied include bleomycin-methotrexate-cisplatin, cisplatin-5-fluorouracil, cisplatin-irinotecan and paclitaxel [16]. Before any treatment it should be taken into account all the possible toxicities of these chemotherapy combinations. In some cases with initially unresectable disease chemotherapy can be administered as neoadjuvant treatment. In particular, in patients with fixed, multiple or bulky nodes (more than 4 cm) we can try to increase the respectability of the disease with a neoadjuvant approach. One chemotherapy combination that has been studied in this setting was ifosfamide-paclitaxel-cisplatin and the response rate was around 50 % while 73 % of patients managed to undergo surgery at the end [17]. In future, more clinical trials not only with classical chemotherapy but also with novel targeted agents may demonstrate better outcomes for patients with advanced penile cancer.

## **48.8 Radiation Therapy**

Radical Radiotherapy (external beam or interstitial brachytherapy) is effective in achieving loco-regional control.

### 48.8.1 External Beam Radiation Therapy

The primary advantage of megavoltage EBRT is penis preservation. If indicated, circumcision must be performed before the start of EBRT, in order to minimize radiation-induced toxicity. A smaller daily fraction size (1.8–2.0 Gy) and a higher total dose (60–65 Gy with the last 5–10 Gy delivered as a boost) are preferable to avoid soft tissue fibrosis and necrosis [1].

EBRT for clinically negative inguinal lymph nodes represents an important component of optimal therapeutic management of microscopic tumor spread. More than 20 % of patients will develop metastatic nodes. If clinical and radiographic confirms a NO disease, the dose to these nodes may be limited to 50 Gy. Grossly metastatic nodes can be removed surgically either before or after inguinal EBRT. Postoperative EBRT to both groins contributes to increase loco regional tumor control. The irradiated area should include inguinal, external and internal iliac lymph nodes. In palpable lymph nodes, doses of approximately 70–75 Gy/1.8–2.0 Gy per fraction with reducing fields (after 50 Gy) should be considered [1].

Langsenlehner T et al. [18] assessed retrospectively the outcome of 24 patients treated with adjuvant EBRT (n=22) and 192Ir high-dose-rate BT (n=2) following total penectomy (n=7), partial penectomy (n=10), or local excision (n=7). In 14 patients, irradiation was delivered after incomplete tumor resection. In 20 cases the planning target volume (PTV) included the regional lymph nodes. Median total dose of EBRT was 56 Gy/1.8–2 Gy (range, 50–60 Gy). BT was given with a total dose of 45 Gy/3 Gy. EBRT was a successful modality of treatment in terms of organ preservation and LC after microscopically incomplete operation. EBRT of the regional lymph nodes was considered in case of high-risk features and following excision of extensive lymph node involvement. The 5-years LC rate was 74.8 %, the 5-years metastases-free survival and PFS rates were 86.7 % and 64.5 %, respectively. The 5-years CSS and OS rates were 84.3 and 56.6 %, respectively.

Johnson TV et al. [19, 20] queried 17 SEER (Surveillance, Epidemiology, and End Results) registries and they found that high grade ( $p<0.001$ ), T classification ( $p=0.010$ ), and adjuvant EBRT ( $p=0.004$ ) were significant predictors of OS. In particular, EBRT after lymphadenectomy was associated with increased OS (HR, 0.58; 95 % CI, 0.41–0.84).

Burt LM et al. [21] evaluated the stage distribution and outcomes for radiotherapy and surgery in a U.S. population database. By multivariable analysis grade 2–3, T3 stage, and metastatic lymph nodes were adverse prognostic factors for CSS. The authors concluded that adjuvant chemo radiation to the inguinal LN and pelvis should be strongly considered for any node positive patient after lymphadenectomy. Even if improved OS or CSS is not achieved with adjuvant EBRT, there may still be benefit of its use in reducing local failures (LF) and the concomitant morbidity of failing to achieve LC within the pelvis and groin.

As in squamous tumors of other sites that drain to the inguinal regions, patients with multiple positive nodes or extra capsular spread should be offered postoperative EBRT [22].

### 48.8.2 Brachytherapy

Brachytherapy (BT) may be an alternative, effective and conservative treatment modality to amputation for T1 and T2 tumors <4 cm in size, located on the glans [23].

Delaunay et al. [24] evaluated the oncologic outcomes, sexual function, and the sexual behavior of 47 patients treated by BT (192Ir) for cancer of the penis. The authors investigated into their sexuality by means of a questionnaire and found that BT had a moderated impact on the sexual functions and the sexual behavior of the patients. The specific survival and the disease-free survival at 5 years was 87.6 % and 84 %, respectively. Sixty-six percent of the patients preserved their penis, 58.8 % remained sexually active after treatment and 94.4 % had erections after treatment. The main predictive factor was age.

De Crevoisier R et al. [23] analyzed the results of interstitial low-dose-rate BT for squamous cell carcinoma, confined to the glans in a total of 144 patients. Inguinal nodal dissection was performed in 19 % of patients (all N negative). After circumcision, BT was performed using the hypodermic needle technique. Median iridium length per patient was 24 cm (range, 4–108) and median dose was 65 Gy (range, 37–75). Median treated volume was 22 cm<sup>3</sup> (range, 5–110) and median reference isodose rate was 0.4 Gy/h (range, 0.2–1.2). With a median follow-up of 5.7 years, the 10-year penile recurrence, inguinal lymph node recurrence, and inguinal nodal metastasis rates were 20 %, 11 %, and 6 %, respectively. The 10-year probability of avoiding penile surgery (for complications or local recurrence) was 72 % and the cancer-specific survival rate was 92 %. Diameter of tumor was a risk factor of recurrence ( $p=0.02$ ). Salvage local treatment was effective. Delayed complications included stenosis, necrosis, fibrosis and ulceration. The 10-year painful ulceration and stenosis risk rates were 26 % and 29 %, respectively. Seven patients required excision for necrosis. Treated volume and reference isodose rate significantly increased the risk of complications and dose rate should be limited to decrease toxicity.

Hasan S et al. [25] presented a meta-analysis from the American Brachytherapy Society, comparing the overall survival (OS) and local control (LC) rates between penectomy and brachytherapy. Nineteen retrospective studies were published between the years 1984–2012, and detailed OS and LC were collected. A total of 2,178 patients, with a median age of 61 years were included (Surgery: 1505, BT: 673). The BT arm included high dose rate, low dose rate, and pulse dose rate between 50 and 70 Gy (median 65), with or without adjuvant EBRT, chemotherapy, or lymph node dissection. Penectomy with adjuvant EBRT was included in the surgery group, and EBRT with a brachytherapy boost was included in the BT group. While penectomy provided better control (5-year LC rate of 84 % vs. 79 % with BT), there was no survival benefit (5-years OS with BT was 73 % vs. 76 % with surgery). In early stage tumors there was no survival or control difference. Among the surgery patients in a Stage I/II, the 5-years OS and LC was 80 % and 86 %, respectively. Of the 209 early stage patients who received brachytherapy, the 5-year OS was 79 % and LC was 84 %. Chi-square testing demonstrated no



difference for either OS or LC for an early stage disease. The organ preservation rate for BT treatment was 74 %. In most cases failed brachytherapy could be salvaged with surgery.

## 48.9 Program for Follow Up of Patients with Penile Cancer

Most relapses occur in the first 2 years after initial treatment and the early detection of lymph node metastases is of particular value. Monitoring includes clinical examination, chest radiograph and abdominal CT scan. Thus, depending on the initial disease management, the guidelines of the European Association of Urology suggest the following patient monitoring program:

1. Conservative treatment: Examination every 2 months the first and second year, every 3 months the third year and every 6 months the fourth-fifth year.
2. Partial or total penectomy: Examination every 4 months in the first and second year, every 6 months the third year and each time the fourth-fifth year.
3. After lymphadenectomy with negative (–) lymph nodes examination should be held every 4 months the first year and every 6 months the second year and then is not necessary.
4. After lymphadenectomy with (+) lymph nodes examination should be held according to the protocol of the hospital.

In conclusion penile carcinoma is one of the few tumors, that lymphadenectomy offers high cure rates even when infiltrated lymph nodes already exist when diagnosed. The pattern and the intervals of follow up are directly related to the initial treatment of the primary tumor and regional lymph node metastases.

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