

Ca Penis II

By-Dr Satyajeet Rath
Prof Kamal Sahni

Role of Circumcision

- Increasing evidence that newborn circumcision has a preventive effect in the development of carcinoma of the penis ¹
- Extremely rare in circumcised Jewish men ²
- Circumcision early in life protects against carcinoma of the penis, but this is not true if the operation is done in adult life ³
- Circumcision is highly effective in preventing the development of penile carcinoma in Nigeria and Uganda ⁴

1. Crawford ED, Dawkins CA. Cancer of the penis. In: , eds. Diagnosis and management of genitourinary cancer. Philadelphia: WB Saunders, 1988:549-563

2. Schoen EJ, Oehrli M, Colby CJ, et al. The highly protective effect of newborn circumcision against invasive penile cancer. Pediatrics 2000;105:E36.

3. Schrek R, Lenowitz H. Etiologic facts in carcinoma of the penis. Cancer Res 1947;7:180-187

4. Owor R. Carcinoma of the penis in Uganda. IARC Sci Publ 1984;63:493-497

Role of Smegma

- Phimosis is common in men suffering from penile carcinoma
- Smegma is carcinogenic in animals, yet the component of the smegma responsible for its carcinogenic effect has not been identified
- Smegma is a byproduct of bacterial action on desquamated epithelial cells in the preputial sac
- It has irritative effect
- Definitive evidence of its role in carcinogenesis is lacking

Relation with HPV

- Approx. half of all carcinomas are HPV related, with the most common serotypes being HPV-16 and HPV-18 ¹
- Boon et al ² observed an increased incidence of cervical carcinoma and penile carcinoma in Bali in a Hindu population in whom circumcision is rare and phimosis in adult males is high
- They suggested that HPV infection, estimated to be present in over 75% of Balinese patients with genital carcinoma, may be a cofactor with impeded postcoital hygiene in genital carcinogenesis
- 2 other studies in US & South America also noted a significantly higher incidence of carcinoma of the cervix in the wives of males with penile carcinoma.

1. Miralles-Guri C, Bruni L, Cubilla AL, et al. Human papillomavirus prevalence and type distribution in penile carcinoma. *J Clin Path* 2009;62:870-878

2. Boon ME, Susanti I, Tasche MJA, et al. Human papillomavirus (HPV)-associated male and female genital carcinomas in a Hindu population: the male as vector and victim. *Cancer* 1989;64:559-565

3. Martínez I. Relationship of squamous cell carcinoma of the cervix uteri to squamous cell carcinoma of the penis. *Cancer* 1979;24:777-780

4. Graham S, Priore R, Graham M, et al. Genital cancer in wives of penile cancer patients. *Cancer* 1979;44:1870-1874

- Quadrivalent vaccine against HPV serotypes 6, 11, 16, and 18 has been approved for females aged 9 to 26 to prevent cervical cancer.
- Based on the demonstrated ability to significantly decrease the incidence of penile lesions (primarily HPV-6 and HPV-11 associated genital warts) in young men, the **U.S. FDA also approved the use of the Quadrivalent vaccine in males aged 9 to 26**
- Potential great benefit to vaccination in countries with much higher penile cancer rates

Natural History

- Most carcinomas of the penis start within the preputial area, arising in the
 - Glans (48%)
 - Prepuce (21%)
 - Glans & prepuce (9%)
 - Coronal sulcus (6%)
 - Shaft (2%)
- In most patients, carcinoma of the penis is characterized by slow locoregional progression
- Patient experiences fear and embarrassment, which probably contributes to delayed diagnosis
- Expeditious diagnosis of all penile lesions should be the rule

- The inguinal lymph nodes are the most common site of metastatic spread
- Pathologic evidence of nodal metastases is reported in
 - about 35% of all patients
 - in approximately 50% of those with palpable lymph nodes
- Distant metastases are uncommon (about 10%) usually occur in patients with inguinal lymph node involvement.
- Patients often die of septic complications, erosion of large vessels in the groin, or a combination of the two
- Positive lymph nodes metastasis is found in
 - Deeper vertical growth - 82% of cases
 - Superficially spreading scc - 42% of cases

1. de Kernion JB, Tynberg P, Persky L, et al. Carcinoma of the penis. *Cancer* 1973;32:1256-1262

2. Staubitz WJ, Lent MH, Oberkircher OJ. Carcinoma of the penis. *Cancer* 1955;8:371-378

Lymph Node Involvement

- Skin of the penis and prepuce - superficial inguinal nodes
- Glans - to the superficial inguinal nodes or even feed directly to the deep inguinal nodes or even the external iliac group
- Corporal bodies - superficial or deep inguinal nodes or directly to the external iliac nodes

- Then drain to 2nd line LN: Iliac & obturator fossa

- Enlargement of the lymph nodes is often related to inflammatory (infectious) processes.
- Administration of antibiotics over several weeks results in regression of inguinal lymph nodes in a substantial proportion of cases and many have advocated this practice before the status of the regional lymph nodes is definitively assessed

- Conversely, between 20% and 40% of patients with clinically negative inguinal lymph nodes have occult metastases.

Incidence of lymph node involvement

- Depends on:
 - Tumor grade: 30% G1 vs 40% G3
 - Local stage : 60% in pT2 & 75% in pT3-4
 - T1G2: 50% [Naumann BJU 2008]
 - Type of local tumor: Basoloid vs Classic

Table 1 – Frequency of lymph node metastases (percent) in penile cancer by grade and stage, as reported in the literature

Reference	Patients, n	Ta, T1	T2	T3	T4	G1	G2	G3
Ornellas et al [6]	350	18	46	64	50	-	-	-
Horenblas et al [78]	102	14		52		29	46	82
Narayana et al [79]	117	30		56		-	-	-
Solsona et al [80]	66	4	64			19	85	85
Lopes et al [17]	145	50	55	53	29	47.5	64	67
Ficarra et al [9]	175	11	20		64	9		29
Naumann et al [18]	20	50	-	-	-	-	50	-

Predictor of LN met

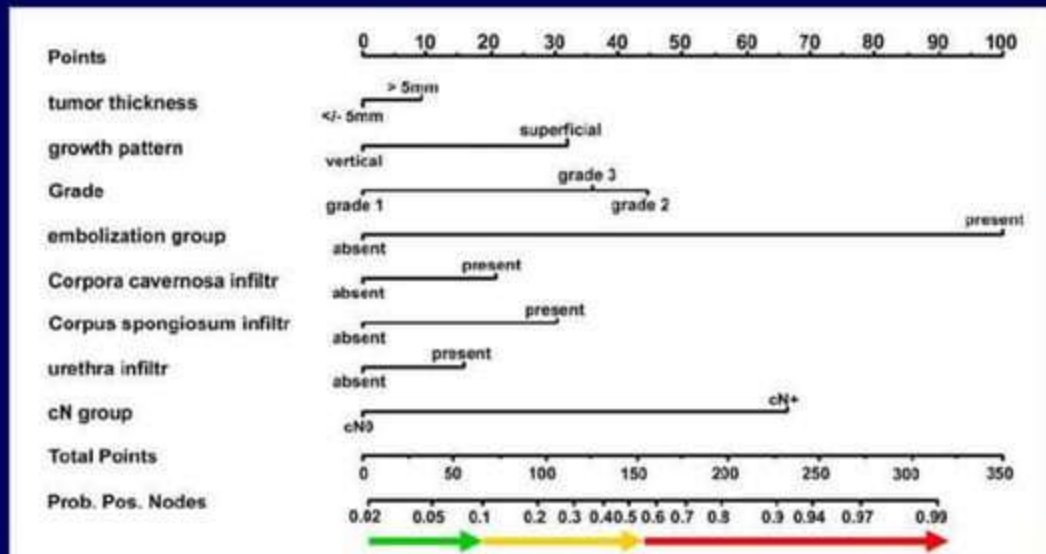
- **Lymphovascular and vascular invasion** was reported to predict LN met
- Risk scoring system: Solsona
- Ficarra nomogram (2006) – 88% accuracy

Pathological extension and grading of the primary tumor

Solsona risk groups	Features	Occult micrometastases (%)
Low	pTa/Tis, pT1G1	0%
Intermediate	pT1G2-3, pT2G1	33%
High	pT2G2-3, >pT2	83%

EAU classification	Features	Occult micrometastases (%)
Low	pTis; TaG1-2; T1G1	0%
Intermediate	pT1G2	30%
High	pT2-3 or G3	73%

Nomogram predictive of pathological Inguinal lymph node involvement



Concordance index 0.876

Clinical Presentation

- May present as either an infiltrative-ulcerative or an exophytic papillary lesion
- Ulceration is also common - approximately half of patients
- In a collective series of 552.¹ patients with penile carcinoma, the presenting symptoms were
 - mass lesions (78%),
 - pain or itching (12%),
 - bleeding (7%),
 - groin mass (7%), and
 - urinary symptoms (4%)
- Priapism as an initial presenting feature or subsequent development occurs in 40% of patients.
- Assessment of the primary lesion may be obscured by the presence of phimosis.
- Secondary infection and associated foul smell are quite common.
- Urethral obstruction

Histo-pathological Type

- SCC (95%)
 1. Usual type (60-70%)
 2. Papillary (7%)
 3. Condylomatous (7%)
 4. Verrucous (7%)
 5. Basaloid (4%)
 6. Sarcomatoid (4%)
- Malignant Melanoma (2%)
- Basal cell carcinoma (2%)
- Extra-mammary Paget's disease (adenoCa from penile skin)
- Sarcoma

Differentiation Grading Systems for SCC

- **Broders' grading** : Divided into 4 grade (1921)
 - Define the level of differentiation based on
 - Keratinization
 - Nuclear pleomorphism
 - Number of mitosis
 - 80 % of the Ca penis is low grade lesion (Gd 1 and 2)
 - 20% Gd 3 and 4
- **Maiche grading** : divided into 3 grade Maiche 1991
 - Correlate with 5 year survival

Grade 1	80%
Grade 2,3	50%
Grade 4	30%

Premalignant Lesions

- Leukoplakia
 - presence of solitary or multiple whitish plaques involving the glans or prepuce in the setting of chronic or recurrent balanoposthitis

- Balanitis Xerotica Obliterans
 - inflammatory condition of the glans and prepuce
 - a form of lichen sclerosis isolated to the penis
 - scaly, indurated, whitish plaque that produces significant phimosis and meatal stenosis
 - lesion is typically benign

- Buschke-Löwenstein Tumor
 - a giant condyloma acuminatum that has a good prognosis
 - does not metastasize
 - viral etiology has been proposed, with identification of HPV-6 and -11 in some tumors

- Bowen disease
 - squamous cell carcinoma in situ that may involve the shaft of the penis as well as the hairy skin of the inguinal and suprapubic area.
 - Clinically, the lesion is a solitary, dull-red plaque with areas of crusting and oozing.
 - Approximately 25% to 50% of patients with this disease have a concomitant visceral malignancy
-
- Erythroplasia of Queyrat
 - epidermoid carcinoma in situ that involves the mucosal or mucocutaneous areas of the prepuce or glans
 - appears as a reddened, elevated, or ulcerated lesion.

Cancers metastatic to the penis

- Most common neoplasms metastasizing to the penis are from the genitourinary organs, followed by the gastrointestinal and respiratory systems
- The predominant cell type is carcinoma, occurring in 93%

Site of Primary Malignancy	Number of Patients
Genitourinary Tract	
Bladder	65
Prostate	65
Kidney	23
Testis	10
Ureter	1
Gastrointestinal Tract	
Rectum/sigmoid	34
Colon	1
Anus	1
Liver	1
Pancreas	1
Respiratory Tract	
Lungs	8
Nasopharynx	1
Other	
Lymphosarcoma/reticulum cell sarcoma	4
Bone	2
Burkitt's lymphoma	1
Skin (malignant melanoma)	1

From Powell BL, Craig JB, Muss HB. Secondary malignancies of the penis and epididymis: a case report and review of the literature. *J Clin Oncol* 1985;3:110-116; reprinted with permission, copyright 1985 American Society of Clinical Oncology.

Diagnosis

- History - Age, Previous duration of phimosis, LUTS, Smoking history, Sexual history
- Physical examination of the genitalia and inguinal nodes
 - to ascertain local extent of the lesion and the presence of inguinal adenopathy
- Approximately 50% of patients with penile cancer present with palpable inguinal nodes
- Only half of these patients will have metastatic disease, with the remainder having inflammatory adenopathy secondary to infection of the primary lesion
- The most common distant metastatic sites are the lung, bone, and liver
- After biopsy confirmation of the lesion, no further radiologic workup is generally needed in patients with early-stage disease and the absence of inguinal adenopathy on examination or other worrisome symptoms

Imaging

- USG, 7.5 MHz
 - Tumor appears as hypoechoic lesion
 - Adv : detect corpus cavernosal invasion with sensitivity of 100 %
 - Disadv: Cant differentiate Ta from T1
- Abdominal and pelvic CT scanning is recommended to evaluate the inguinal nodes.
- In patients with known inguinal metastases, CT-guided biopsy of enlarged pelvic nodes should be done.
- MRI may be helpful in cases that are difficult to stage clinically, with a positive predictive value for invasion of the corpora cavernosa of 75%
- Any patient who presents with phimosis and chronic discharge, bleeding, balanitis, or swelling in the region of the coronal sulcus or glans under an unretractable foreskin should have a dorsal slit of the foreskin to allow inspection of the glans and should preferably have a full circumcision

Jackson Staging System (1966)

1. Confined to the glans or prepuce
2. Invasion into shaft or corpora
3. Operable inguinal lymph node metastasis
4. Tumour involves adjacent structures ; inoperable inguinal lymph nodes

AJCC 7th - T Staging

- TX : Primary tumor cannot be assessed
- T0 : No evidence of primary tumor
- Tis : Carcinoma in situ

- Ta : Noninvasive verrucous carcinoma
(Broad pushing penetration (invasion) is permitted ; destructive invasion is against this diagnosis)

- T1a Tumor invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3-4)
- T1b : Tumor invades subepithelial connective tissue with lymph vascular invasion or is poorly differentiated

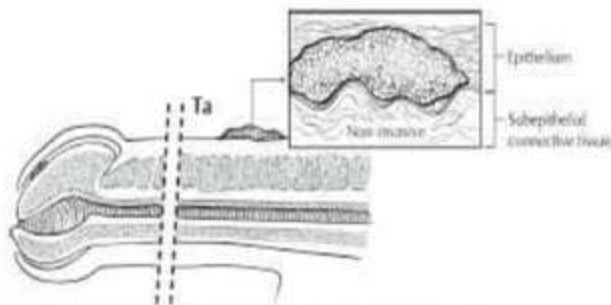


FIGURE 40.1. Ta: Noninvasive verrucous carcinoma.

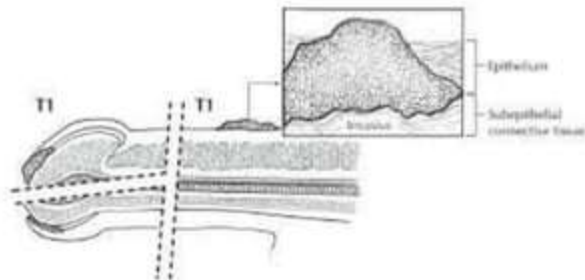


FIGURE 40.2. T1: Tumor invading subepithelial connective tissue; T1a: no vascular invasion and not poorly differentiated; and T1b: high grade and/or poorly differentiated.

- T2 : Tumor invades corpus spongiosum or cavernosum

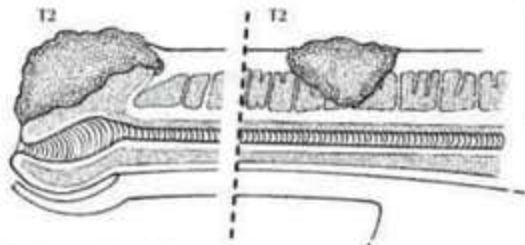


FIGURE 40.3. T2: Tumor invading corpus spongiosum or cavernosum.

- T3 : Tumor invades urethra

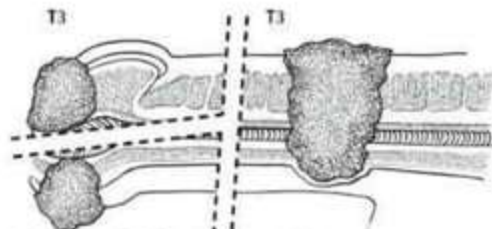


FIGURE 40.4. T3: Tumor invading urethra.

- T4 : Tumor invades other adjacent structures

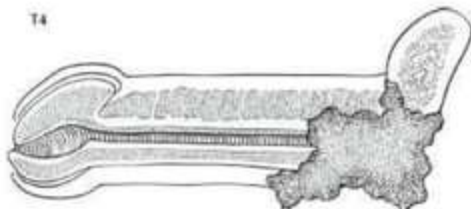


FIGURE 40.5. T4: Tumor invading other adjacent structures including prostate.

Regional Lymph Nodes (N)

Clinical Stage Definition

(based on palpation and imaging)

- cNX : Regional lymph nodes cannot be assessed
- cN0 : No palpable or visibly enlarged inguinal lymph nodes
- cN1 : Palpable **mobile** unilateral inguinal lymph node
- cN2 : Palpable **mobile** multiple or bilateral inguinal lymph nodes
- cN3 : Palpable **fixed** inguinal nodal mass **or pelvic lymphadenopathy** unilateral or bilateral

Pathologic Stage Definition

(based on surgical biopsy and excision)

- pNX : Regional lymph nodes cannot be assessed
- pN0 : No regional lymph node metastasis
- pN1 : Metastasis in a single inguinal lymph node
- pN2 : Metastasis in multiple or bilateral inguinal lymph nodes
- pN3 : Extranodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral

- Distant Metastasis (M)

- M0 : No distant metastasis
- M1 : Distant metastasis*

- * Lymph node metastasis outside of the true pelvis in addition to visceral or bone sites.

- Grading

- GX Grade cannot be assessed
- G1 Well differentiated
- G2 Moderately differentiated
- G3 Poorly differentiated
- G4 Undifferentiated

Stage Grouping			
0	Tis	NO	MO
	Ta	NO	MO
I	T1a	NO	MO
II	T1b	NO	MO
	T2	NO	MO
	T3	NO	MO
IIIa	T1-3	N1	MO
IIIb	T1-3	N2	MO
IV	T4	Any N	MO
	Any T	N3	MO
	Any T	Any N	M1

* Most malignant penile tumors are well-differentiated squamous cell carcinomas

THANK YOU