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European Association of Urology

Guidelines – Penile Cancer

EAU Penile Cancer Guidelines 2009

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Abstract

Context: Squamous cell carcinoma (SCC) of the penis is a relatively rare but ominous disease.
Objective: To present a condensed version of the updated 2009 European Association of Urology (EAU) guidelines on penile SCC.
Evidence acquisition: We performed a literature search of new data available up to December 2009. No randomized study was found; consequently, level of evidence (LE) and grade of recommendations (GR) are low.
Evidence synthesis: More insight was gained into the etiology of SCC of the penis, together with improved staging and treatment: *Human papillomavirus 16* plays an etiologic role in approximately 40–50% of cases. Similarities in etiology with SCC of the head and neck, the female genitalia, and the anal canal have been found. Improved diagnostics allowed earlier diagnosis, leading to more conservative treatments. Adjuvant and neoadjuvant chemotherapy showed promising results in patients with advanced or recurrent disease. Centralization of the disease contributed to standardization and rapid diffusion of new treatments with improved results and increased organ preservation.
Conclusions: Improvements in the management of SCC of the penis are reflected in changes in the guidelines, but the rarity of the disease precluded randomized studies, leading to low level of evidence and grade of recommendation.

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1. Introduction

The European Association of Urology (EAU) Guidelines Group on Penile Cancer has updated this guidelines document to assist medical professionals in the management of the disease. The penile cancer guidelines were first published in 2001 and updated in 2004 and 2009 [1]. In recent years, significant progress was made in better understanding the natural history of the disease and staging and treatment have been improved.

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Table 1 – Levels of evidence*

Evidence level	Type of evidence
1a	Evidence obtained from meta-analysis of randomized trials
1b	Evidence obtained from at least one randomized trial
2a	Evidence obtained from one well-designed controlled study without randomization
2b	Evidence obtained from at least one other type of well-designed quasiexperimental study
3	Evidence obtained from well-designed nonexperimental studies, such as comparative studies, correlation studies, and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

* Modified from Phillips et al. [3].

Table 2 – Grades of guideline recommendations*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
B	Based on well-conducted clinical studies but without randomized clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

* Modified from Phillips et al. [3].

A literature search of publications through December 2009 was carried out by the chairman and all members of the Penile Cancer Consensus Group: PubMed provided 997 specific abstracts on *SCC of the penis* and 4950 miscellaneous papers on *penile cancer*. No Cochrane reviews or randomized studies were found. Only one peer-reviewed document was published [2]: the physician data query on penile cancer treatment (health professional version) published by the National Cancer Institute at the US National Institutes of Health.

References, statements, and guideline recommendations have been assessed according to their level of scientific evidence and grades of recommendation (GR) have been assigned according to a rating scheme modified from the Oxford Center for Evidence-based Medicine (Tables 1 and 2) [3]. Maximal level of evidence (LE) was 2b, which accounts for the low grading of recommendations.

2. Evidence acquisition

A systematic literature search on *penile cancer* was performed by all members of the EAU Penile Cancer Working Group covering the time-span 2005-Dec 2008.

At the onset of the project each member was assigned one or two topics in accordance with their particular expertise. Each panel member was teamed up with another panel member who acted as a reviewer of their section. The panel decided to avoid rare diseases and to restrict the guidelines to squamous cell carcinoma (SCC) only. Since new publications became available in the first 2 yr the initial literature acquisition resulted in a first draft for discussion in 2008. This document was reviewed and updated by the panel and published in the 2009 edition of the EAU guidelines book and as an ultra-short (pocket) edition at the EAU Annual Congress in Stockholm, Sweden. For this European Urology document an updating search was performed covering the period between December 2008 and December 2009.

3. Evidence synthesis

3.1. Epidemiology

Penile SCC is a relatively rare disease. It usually originates in the epithelium of the inner prepuce and glans. In Western countries, penile cancer is uncommon, but it is lightly increasing with important variations within several European regions, ranging from 0.5 to 1.6 per 100 000 males annually (Fig. 1). Incidence in the United States is affected by race and ethnicity; it is low for Asia-Pacific Islanders and American Indians and is highest for Hispanics and southern Blacks [4].

In the non-Western world, the incidence rate of penile cancer is much higher and can reach 10% of all malignant diseases in men, ranging from an age-adjusted incidence of 0.7–3.0 per 100 000 men in India to 8.3 per 100 000 men in Brazil and even higher in Uganda [4].

Important risk factors include social and cultural habits, hygiene, and religious practices [5]. Penile carcinoma is rare in communities that practice circumcision in newborns or before puberty (eg, Jews, Muslims, Ibos of Nigeria). Circumcision in adults does not prevent penile cancer but allows early diagnosis [6]. In Western countries, incidence increased slightly during the 1980s and 1990s. The incidence rate increases with age, although the disease has also been reported in young men. For non-Western countries, the peak incidence occurs in the early fifties [4].

3.2. Risk factors

Strong risk factors (odds ratio: >10) identified by case-control studies include:

- Phimosis [5]
- Chronic inflammatory conditions such as balanoposthitis and lichen sclerosus et atrophicus (balanitis xerotica obliterans) [5]
- Treatment with sporalene and ultraviolet A phototherapy [5]
- Sexual history (multiple partners, early age at first intercourse) [6]
- History of condylomata (associated with a 3- to 5-fold increased risk of penile cancer)
- Smoking [6].

In many case series, human papillomavirus (HPV) DNA was identified in 70–100% of intraepithelial neoplasia and in 40–50% of cases with invasive penile cancer. These results were confirmed by a population-based case control study [6]. HPV DNA was detected in 80% of tumor specimens, of which 69% were positive for *Human papillomavirus 16* (HPV-16). The virus plays an important role in oncogenesis

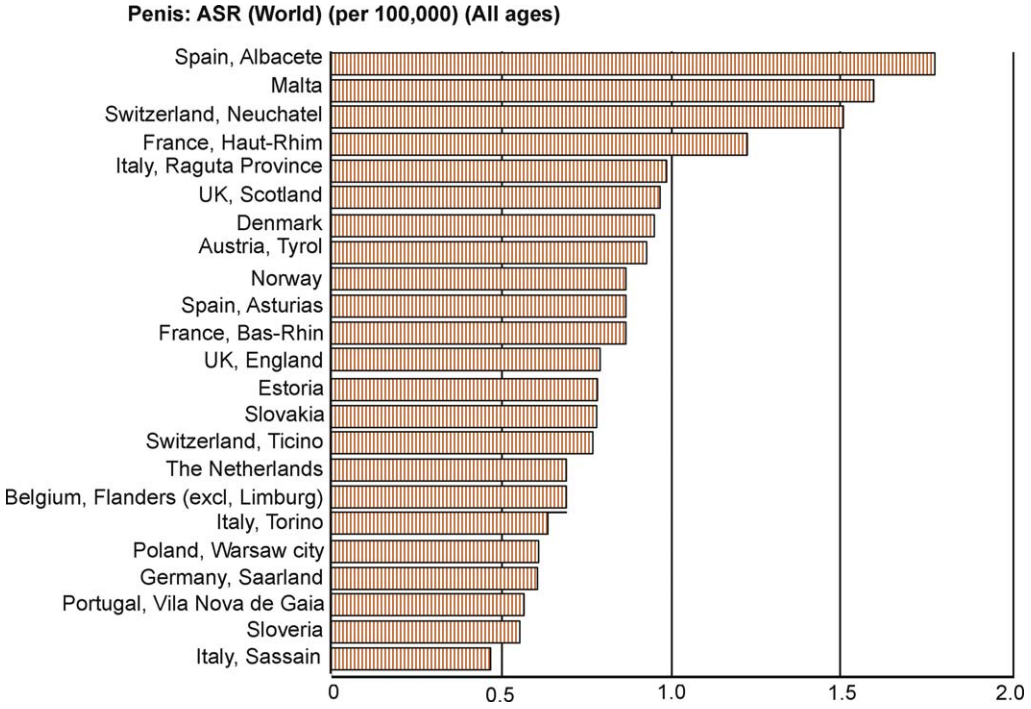

Fig. 1 – Annual incidence rate (world standardized) by European region/country. Reproduced with permission from IARC Press [4].

through interaction with oncogenes and tumor suppressor genes (tumor protein 53 [p53] and retinoblastoma [RB]) [7].

Patients with condylomata acuminata have an increased risk of cancer for vulva, vagina, penis, and anus [8]. HPV-16 has a causal role in 70% of cancers of the cervix, the vagina, and the anus and in about 40–50% of cancers of the vulva, the penis, and the oropharynx.

In June 2006, the US Food and Drug Administration (FDA) licensed the first vaccine to prevent cervical cancer and other HPV-associated diseases in women [9]. The vaccine protects against infection with HPV-6, -11, -16, and -18. The recommended age for vaccination in females is 11–12 yr. Vaccination against HPV has also been proposed for males [10], but must wait for the results of female HPV vaccination.

Data on the prognostic significance of HPV DNA in penile cancer are conflicting. Although one study did not show any effect on survival, another reported 93% survival in the high-risk HPV–positive group versus 78% in the high-risk HPV–negative group (log rank test, $p = 0.03$) [11].

3.3. *Classification and pathology*

3.3.1. *TNM classification*

The new, 2009, Tumor Node Metastasis (TNM) classification for penile cancer includes a change for the T1 category [12] (Table 3). This classification needs a further update for the definition of the T2 category*. A recent publication showed that the prognosis for corpus spongiosum invasion is much better than for corpora cavernosa invasion [13]. A new TNM classification was proposed [13].

3.3.2. *Pathology*

SCC accounts for >95% of cases of cancer of the penis, with malignant melanoma and basal cell carcinoma accounting for another 3%. It is assumed that SCC is preceded by premalignant lesions (Table 4). Different types and varying growth patterns of penile SCC have been identified (Table 5).

Table 3 – 2009 TNM clinical and pathological classification of penile cancer [12], presented in Tables 3a and 3b.

Table 3a – Clinical classification

T	**Primary tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Non-invasive verrucous carcinoma, not associated with destructive invasion
T1	Tumor invades subepithelial connective tissue
T1a	without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)
T1b	with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)
T2*	Tumor invades corpus spongiosum/corpora cavernosa
T3	Tumor invades urethra
T4	Tumor invades other adjacent structures
N	**Regional lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph node
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral
M	**Distant metastases**
M0	No distant metastasis
M1	Distant metastasis

Table 3b – Pathological classification

pN	**Regional lymph nodes**
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Intranodal metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of regional lymph node metastasis
pM	**Distant metastases**
pM0	No distant metastasis
pM1	Distant metastasis
G	**Histopathological Grading**
Gx	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated/undifferentiated

The pT cathegories correspond to the T categoris. The pN cathegories are based upon biopsy, or surgical excision.

Table 4 – Premalignant lesions in squamous cell carcinoma (SCC) of the penis

Lesions sporadically associated with SCC of the penis
Cutaneous horn
Bowenoid papulosis
Lesion at intermediate risk of developing SCC
Balanitis xerotica obliterans (lichen sclerosus et atrophicus)
Lesions at high risk of developing SCC of the penis*
Penile intraepithelial neoplasia (carcinoma in situ):
-Erythroplasia of Queyrat
-Bowen's disease

* Up to one-third will transform to invasive SCC.

3.4. Penile biopsy and histology

A diagnostic biopsy of the pathologic tissue is routinely performed. An excisional biopsy is advised when there is doubt about the exact nature of the lesion. Histologic subtypes carry different risks of developing metastatic lymph nodes; sarcomatoid tumors have the poorest prognosis, with 89% risk of lymph node invasion [14].

Table 5 – Pathologic classification of squamous cell carcinoma (SCC) of the penis

Types of SCC
Classic
Basaloid
Verrucous and its varieties:
-Warty (condylomatous) carcinoma
-Verrucous carcinoma
-Papillary carcinoma
-Hybrid verrucous carcinoma
-Mixed carcinomas (warty basaloid, adenobasaloid carcinoma)
Sarcomatoid
Adenosquamous
Growth patterns of SCC
Superficial spread
Nodular or vertical-phase growth
Verrucous
Differentiation grading systems for SCC
Broder's grading system [65]
Maiche's system score [66]

Table 6 – Guidelines on the diagnosis and staging of penile cancer (GR: C)

Primary tumor
• Physical examination recording morphologic and physical characteristics of the lesion
• Cytological and/or histological diagnosis
Regional lymph nodes disease
• Physical examination of both groins, recording nodal morphological and physical characteristics
- If nodes are non-palpable, DSNB is indicated; if DSNB not available, ultrasound-guided FNAC/risk factors
- If nodes are palpable, FNAC for cytological diagnosis
Regional metastases (inguinal and pelvic nodes)
• A pelvic CT scan/PET-CT scan is indicated in patients with metastatic inguinal nodes
Distant metastases (beside inguinal and pelvic nodes)
• PET-CT scan also allows evidence of distant metastasis
• If PET-CT is not available, abdominal CT scan and chest x-ray are advisable, and in symptomatic M1 patients a bone scan is also advisable
Biological laboratory determinations for penile cancer are investigational and not for clinical use

CT = computed tomography; DSNB = dynamic sentinel node biopsy; GR = grade of recommendation; FNAC = fine-needle aspiration cytology; PET = positron emission tomography.

Invasive patterns are correlated with lymph node metastases—23% of positive lymph nodes appear in the nodular pattern and 65% appear in the infiltrative pattern [14].

3.5. Diagnosis and staging

Accurate staging of the primary tumor and regional lymph nodes enables appropriate treatment (Table 6).

3.5.1. Primary lesion

Physical examination includes:

- Diameter of the penile lesions or suspicious areas
- Location and number of lesions
- Morphology of lesions (papillary, nodular, ulcerous, flat)
- Relationship of lesions to other structures (eg, submucosa, tunica albuginea, urethra, corpus spongiosum, corpus cavernosum)
- Color and boundaries of lesions
- Penis length and expected residual length if penectomy has to be performed.

Infiltration into the corpora can be assessed by physical examination. Magnetic resonance imaging (MRI; in combination with an artificial erection with prostaglandin E1) may help identify the depth of invasion of corpora and determine whether conservative surgery (glansectomy only) can be performed [15] (LE: 3).

3.5.2. Regional lymph nodes

Penile cancer drains primarily to the inguinal nodes [16]. A recent single photon emission computed tomography (SPECT)–computed tomography (CT) imaging study showed that all sentinel nodes are located in the superior and central inguinal Daseler's zones, with most found in the

medial superior zone [17]. No direct lymphatic drainage was observed from the penis to the inferior two regions of the groin, and no direct drainage to the pelvic nodes was visualized [17] (LE: 2b).

3.5.2.1. Nonpalpable nodes and risk factors. In the absence of palpable nodes, an inguinal ultrasound (7.5 mHz) may reveal abnormal nodes and can be used as a guide for fine-needle aspiration biopsy [18].

Traditionally, histopathologic prognostic factors have been used to select high-risk clinical N0 patients for lymphadenectomy (LAD). The 2004 EAU guidelines recommended modified LAD in clinical N0 patients with T1G2 nodular growth or vascular invasion and radical LAD in any T1G3 tumors and in all tumors T2 or higher [1] (grade of recommendation [GR]: C).

Today, presence of lymph node metastases may be predicted by several tumor characteristics other than T and G categories. Risk factors for lymph node metastases include pathological subtypes, perineural invasion, lymphovascular invasion, tumor depth or thickness, anatomic site, size, and growth pattern, with perineural invasion, vascular invasion, and high histologic grade being the most important predictors [14] (LE: 2b).

Nomograms have been proposed to estimate the cumulative risk of metastatic involvement using clinical and pathologic parameters [24]; the concordance index was 0.728 and 0.747, respectively, in the two models (LE: 2b).

A sentinel node biopsy (SNB) was not recommended initially because of a high rate of false-negative results [19]. However, a subsequent report demonstrated that dynamic SNB (DSNB; using isosulfan blue and/or technetium Tc 99m–colloid sulfur) improved survival versus a "wait and see" policy and reduced morbidity compared to prophylactic inguinal LAD [20,21]. An update demonstrated that DSNB has 100% specificity and 95% sensitivity [22]. Moreover, a two-center evaluation of DSNB demonstrated the reproducibility of the technique [23] (LE: 2b).

3.5.2.2. Palpable nodes. Lymph node metastases in palpable nodes can be diagnosed using a percutaneous fine needle aspiration biopsy for cytology and/or histology. In case of a negative biopsy and clinically suspicious nodes, a repeat biopsy is advised [27] (GR: C). At the time of diagnosis of penile cancer, as much as 50% of palpable inguinal nodes are caused by inflammatory reactions; however, nodes that become palpable during follow-up are due to metastasis in nearly 100% of cases [26] (LE: 2b).

For imaging of inguinal lymph nodes, CT scan is mostly used, despite low sensitivity (36%). Lymphotropic nanoparticle–enhanced MRI (LN-MRI) was promising [28], but positron emission tomography (PET)–CT demonstrated excellent positive and negative predictive values of 94% and 96%, respectively, thanks to increased sensitivity [25] (LE: 3).

3.5.3. Distant metastases

An assessment of pelvic metastasis is to be performed in patients with proven tumor-positive inguinal nodes because pelvic metastases do not occur in the absence of metastatic inguinal nodes [17,25,30,31]. The recent use of PET-CT scanning proved to be quite reliable [25,29], and metastases in more distant sites are documented. The detection of pelvic metastases and of more distant metastases has a considerable impact on therapy and prognosis [29].

3.5.4. Molecular biology

Molecular markers are not of clinical use in SCC of the penis. SCC antigen is not sensitive in small tumor burden and has little prognostic significance for survival after surgery [32]. Lymph node metastases are also correlated with the expression of p53, Ki-67, and E-cadherin, but these markers are not useful in clinical practice [33].

3.6. Treatment

The primary tumor and regional lymph nodes are usually treated separately. Although it is important to avoid overtreatment, leading to loss of penile tissue and to side effects of unnecessary LAD, it is essential to remove all cancerous tissue into healthy margins.

Table 7 – Guidelines on treatment strategies for penile cancer

Primary tumor	Conservative treatment is to be considered whenever possible	LE	GR
Category Tis, Ta, Tla (G1, G2)	CO_2 or Nd:YAG laser surgery, wide local excision, glans resurfacing, or glans resection, depending on size and location of the tumor	2b	C
	Mohs' micrographic surgery or photodynamic therapy for well differentiated (G1) superficial lesions	3	
Categories: T1b (G3) and T2 (glans only)	Glansectomy, with or without tips amputation or reconstruction	2b	B
Category T2 (invasion of the corpora)	Partial amputation	2b	B
Category T3 invasion of urethra	Total amputation and perineal urethrostomy	2b	B
Category T4 (other adj. structures)	Eligible patients: neoadjuvant chemotherapy followed by surgery in responders. Alternative: external radiation	3	C
Local disease recurrence after conservative therapy	Salvage surgery, consisting of penis-sparing treatment in small recurrences Larger recurrence: some form of amputation	2b	B
Radiotherapy	Organ-preserving treatment in selected patients with T1–2 glans or coronal sulcus lesions <4 cm	2b	B
–	Palliation in advanced or metastatic disease unresponsive to chemotherapy	2	C

CO_2 = carbon dioxide; Nd:YAG = neodymium:yttrium-aluminum-garnet.

3.6.1. Primary tumor

Guidelines on treatment strategies for primary tumor in penile cancer are outlined in Table 7. For small lesions, a penis-preserving strategy is recommended (GR: B). There is a variety of modalities, which have not been compared in a scientifically rigorous way, and recommendation based on published data is difficult. However, *treatment choice is influenced by size of the tumor, its position on the glans or in the corpora, and experience*. There are no documented differences in the local recurrence rate among surgery, laser therapy, and radiation. Although conservative surgery improves quality of life (QoL), the risk of local recurrence is higher than after ablative surgery (27% vs 5%).

The pathologic assessment of surgical margins is essential to guarantee tumor-free margins [34]. Tumor-positive margins lead inevitably to local recurrences; total removal of the glans (glansectomy) and prepuce has the lowest recurrence rate of treatment modalities for small penile lesions (2%) [35].

3.6.1.1. Categories Tis, Ta, and T1a. Superficial lesions can be treated with the following penis-sparing techniques:

- Local excision with or without circumcision (LE: 3)
- Laser therapy with carbon dioxide (CO_2; peniscopically controlled) or neodymium:yttrium-aluminum-garnet (Nd:YAG) laser [36,37] (LE: 2b)
- Mohs micrographic surgery (for verrucous carcinoma) [38] (LE: 3)
- Photodynamic therapy (for superficial lesions) [39] (LE: 3)
- Topical therapy with 5-fluorouracil (5-FU) imiquimod 5% cream and other agents are sporadically reported for superficial lesions (several recurrences) (LE: 4).

T1b tumors of the glans with deeper infiltration (>1 mm) can be treated with the following techniques:

- Wide local (laser) excision plus reconstructive surgery or total glans resurfacing with or without skin transplantation [40] (LE: 2b)
- Neoadjuvant chemotherapy (vinblastine, bleomycin, and methotrexate [VBM]) followed by CO_2 laser excision and spontaneous glans reepitalization [36] (LE: 2b)
- Radiotherapy (see section 3.6.1.6.)
- Glansectomy [35,40,41] (LE: 2b).

Conservative treatment may be less suitable in cases of multifocal lesions, which are responsible for 15% of recurrences. Total treatment of the glans surface combined with concomitant circumcision is recommended to avoid multiple recurrences [36] (GR: C).

Negative surgical margins are imperative when using penile-conserving treatments. Pathologic assessment of the surgical margins is recommended (GR: C). In general, a margin of ≥3 mm is considered safe [34].

3.6.1.2. Category T2 (limited to the glans). Total glansectomy, with or without resurfacing of the corporeal heads, is recommended [40,42] (LE: 2b; GR: B). Radiotherapy is also recommended (see section 3.6.1.6). Consider partial amputation in patients who are unfit for more conservative reconstructive surgery [41] (GR: C).

3.6.1.3. Local disease recurrence after conservative surgery. A second conservative procedure is advised if there is no corpora cavernosa invasion [35–40] GR: C]. If there is a large or deep infiltrating recurrence, partial or total amputation is inevitable [43] (GR: B).

3.6.1.4. Category T2 with invasion into the corpora cavernosa. Partial amputation with a tumor-free margin is considered standard treatment [41] (GR: B). A surgical margin of 5–10 mm is considered safe [34]. Reconstruction may alleviate the mutilation [42,44].

3.6.1.5. Categories T3 and T4. These categories of patients are rare (eg, 5% in Europe, l3% in Brazil) [4]. Total penectomy with perineal urethrostomy is standard surgical treatment for T3 tumors [26] (GR: B). Spatulating the urethra is helpful in preventing stenosis. In more advanced disease (T4), neoadjuvant chemotherapy is advised, followed by surgery in responding patients (GR: B; see section 3.6.2.4). Otherwise, adjuvant chemotherapy or consolidating radiation is advised (GR: C; see sections 3.6.2.3 and 3.6.2.5).

3.6.1.6. Radiotherapy. Radiotherapy of the primary tumor is an alternative organ-preserving approach with good results in selected patients with T1–2 lesions <4 cm in diameter [45–48] (LE: 2b).

Best results have been obtained with brachytherapy with local control rates ranging from 70% to 90% [45,47]. Patients with large volume lesions (>4 cm) are not candidates for brachytherapy. A minimum dose of ≥60 Gy is given for both external radiotherapy combined with a brachytherapy boost and brachytherapy alone [45–47]. The penile preservation rate after radiotherapy is approximately 80%. Local failure rates after radiotherapy are higher than after partial penectomy, but salvage surgery can restore local control [48]. The following complications are the most frequent reported: urethral stenosis (20–35%), glans necrosis (10–20%), and late fibrosis of the corpora (LE: 3).

No scientifically sound recommendations can be given regarding surgical procedures versus radiotherapy. Institutional experience and possibilities play an important role in decision making.

3.6.2. Regional lymph nodes

Guidelines on treatment strategies for nodal metastases are presented in Table 8. LAD is the treatment of choice for patients with inguinal lymph node metastases (GR: B). The procedure requires careful skin-flap management, meticulous lymph node dissection, prophylactic antibiotics, compression stockings, and early ambulation. Prolonged lymph leakage, leg and scrotal lymph edema, skin-flap necrosis, and wound infection may occur in 30–70% of patients [26] (LE: 2b). Recent studies show a decrease in

Table 8 – Guidelines on treatment strategies for nodal metastases

Regional lymph nodes	Management of regional lymph nodes is fundamental in the treatment of penile cancer	LE	GR
No palpable inguinal nodes	Tis, TaG1, T1G1 without risk factors: surveillance	2b	B
	T1G2 or higher: DSNB, followed by completion LAD if DSNB is tumor positive	2b	B
	If DSNB not available: LAD based on risk factors or nomograms (see 2004 guidelines [1])	3	C
Palpable inguinal nodes	Ultrasound-guided FNAC Positive biopsy: inguinal LAD on positive side Negative FNAC biopsy: repeat FNAC or excise suspicious nodes; alternative: LAD	2b	B
Pelvic nodes	Pelvic LAD if (1) extranodal metastasis, (2) Cloquet node involved, (3) two or more inguinal node metastases	2b	B
Adjuvant chemotherapy	Patients with more than one intranodal metastases (pN2, pN3) after LAD	2b	B
Patients with fixed or relapsed inguinal nodes	Neoadjuvant chemotherapy followed by surgery	2b	B

DSNB = dynamic sentinel node biopsy; LE = level of evidence; LAD = lymphadenectomy; FNAC = fine-needle aspiration cytology.

complications, suggesting that these procedures should be done by experienced surgeons [49].

3.6.2.1. Management of patients with nonpalpable inguinal nodes. All noninvasive diagnostics miss approximately 20% of microscopic metastases. Additionally, the sensitivity of a published nomogram does not exceed 80% [24] (LE: 2b).

Various risk factors have been helpful in stratifying node-negative patients for lymph node dissection [14,24] (LE: 2b). This approach was the basis for the 2004 recommendations for the management of clinically node-negative patients. In centers without sentinel node diagnostics, these recommendations can still be useful. In addition to these recommendations, T1G2 tumors should be considered high risk based on a recent analysis [50]. The experience from Brazil can be used as a gold standard for survival rates that can only be attained by surgery [49].

Only DSNB has better sensitivity (94%) [22] (LE: 2b). To reliably identify the sentinel nodes, preoperative mapping is essential. Tc 99m nanocolloid is injected the day before; before surgery, patent blue is injected and a γ-ray detection probe is used intraoperatively. A complete inguinal LAD is performed only in tumor-positive patients. The current protocol has a sensitivity of 95% [22]. The technique is now reproducible with a short learning curve [23] (GR: B).

Considering the rarity of the disease and considering the possible improvements in diagnosis and treatment, centralization is recommended. Centralizing patients with penile SCC in 10 centers in the United Kingdom allowed improvement in the cure of the disease within a few years [51].

3.6.2.2. Management of patients with palpable inguinal nodes. Ultrasound-guided fine-needle aspiration biopsy provides an excellent, rapid, and easy way to detect metastatic nodal involvement [18] (LE: 3). In suspected cases with tumor-negative findings, various strategies can be followed: (1) antibiotics are given, (2) fine-needle aspiration biopsy is repeated, (3) a suspected node is surgically removed, and (4) inguinal LAD is performed. DSNB is not reliable in patients with palpable suspected nodes and should not be used [52] (LE: 3); however, SNB can be used for the noninvolved side. In tumor-positive sites, LAD is performed.

In inguinal LAD, significant morbidity has been described. In advanced cases, reconstructive surgery is often necessary for primary wound closure [53].

Modified inguinal LAD is a procedure associated with less morbidity, but reducing the field of dissection increases the possibility of false-negative results. Current knowledge on lymphatic drainage of the penis suggests that a modified LAD should dissect at least the central and both superior Daseler's zones [16,17] (LE: 3).

Because there is no direct lymphatic drainage from penile cancer to the pelvic lymph nodes [17], pelvic LAD is not needed if there is no involvement of inguinal nodes (LE: 3). In contrast, pelvic LAD is recommended if the node of Cloquet or two or more inguinal nodes are involved. The rate of positive pelvic nodes was found to be 23% in cases with more than two positive inguinal nodes and 56% for more than three positive inguinal nodes or if there was extracapsular extent in at least one inguinal node [26,49] (LE: 2b). Pelvic LAD may be performed as a secondary procedure. If bilateral dissection is indicated, it can be performed though a midline suprapubic extraperitoneal incision.

Laparoscopy is unfit for radical surgery.

3.6.2.3. Adjuvant chemotherapy. Adjuvant chemotherapy after resection of nodal metastases has been reported in few small heterogeneous series, but at the National Cancer Institute in Milan, Italy, a long-term disease-free survival (DFS) rate of 84% was obtained in 25 consecutive node-positive patients treated with 12 adjuvant weekly courses of VBM during the period 1979–1990 (54,55) versus only 39% DFS for 38 consecutive patients who underwent radical LAD, with or without complementary radiotherapy, in the period 1960–1978 [54]. Since 1991, categories pN2–3 patients have received three courses of adjuvant cisplatin and 5-FU with lower toxicity and even better results [55] (LE: 2b). Category pN1 patients do not need adjuvant chemotherapy [55] (LE: 2b).

3.6.2.4. Management of patients with fixed or relapsed inguinal nodes. Upfront surgery is not recommended (GR: B) because cure is unlikely, survival is short, and the surgery is usually quite extensive. Upfront chemotherapy seems like a more

rational approach. Multiple regimens have been used in a small number of patients. Cisplatin, methotrexate, and bleomycin (BMP) at Memorial Sloan-Kettering Cancer Center in New York [56] showed promising figures, but a confirmatory study by the Southwest Oncology Group reported unacceptable toxicity and modest results [57]. Leijte et al. [58] reported on 20 patients with five different neoadjuvant chemotherapy regimens in the 1972–2005 period. Responders underwent postchemotherapy surgery with a 37% long-term survival rate. At the MD Anderson Cancer Center [59], combination therapies with paclitaxel, carboplatin or paclitaxel, cisplatin, and ifosfamide were used in seven patients, followed by surgery; four patients were long-term survivors (48–84 mo). None of the three patients treated with BMP achieved significant remission. A preliminary study [60] on taxol combined with cisplatinum and 5-FU reported significant responses in five of six patients with fixed or relapsed inguinal nodes, but only the three who underwent postchemotherapy surgery achieved durable complete remission.

In conclusion, adjuvant chemotherapy is recommended in pN2–3 patients [55] (GR: C) and neoadjuvant chemotherapy followed by radical surgery is advisable in nonresectable or recurrent lymph node metastases [58–60] (GR: C).

3.6.2.5. The role of radiotherapy. Prophylactic radiotherapy in clinical N0 patients is not recommended [61] (GR: C) because of:

- Failure to prevent the development of metastatic lymph nodes
- Complications of radiotherapy
- More difficult follow-up due to fibrotic changes.

Adjuvant radiotherapy may improve locoregional control in patients with extensive metastases and/or extranodal spread, but control is achieved at the cost of severe side effects including severe edema and pain (GR: C).

3.7. Follow-up

The aim of follow-up (Table 9) is to detect early recurrences when they may still be cured. Modern ultrasound imaging is a useful adjunct, with promising results from new imaging modalities such as PET-CT.

The follow-up for patients with penile cancer is directed by the initial treatment. One large series showed that 92.2% of all recurrences occurred within the first 5 yr [62]. All recurrences after 5 yr appeared to be local recurrences only or new primaries.

3.7.1. Primary tumor

Local recurrence has been reported in up to 30% of patients during the first 2 yr following treatment with penile-preserving surgery. Local recurrence rate is independent of type of local therapy and is easily detected by the patient, his partner, or his family doctor and does not affect survival, assuming that early detection and prompt treatment are undertaken [62]. Following penile-preserving treatment, a follow-up visit every 3 mo is advised in the first 2 yr; then, a follow-up every 6 mo is advised, provided that the patient and his partner have been well instructed to examine the penis regularly and to return if any abnormality is observed. A patient must continue to carry out regular self-examination even after a 5-yr follow-up. After amputation, a less frequent time interval of every 6 mo is advised. The risk of local recurrence is not more than 5% [62] (GR: C).

3.7.2. Regional recurrences

Most regional recurrences occur within 2 yr after inguinal LAD or SNB. Stringent follow-up is advised with ultrasound investigation of the groin every 3 mo for 2 yr [62] (GR: C). Patients managed with a wait-and-see policy have a higher risk of recurrence (9%) than patients staged surgically for negative nodes (2.3%), whether performed by traditional LAD or dynamic SNB [62]. Patients treated because of lymph node metastases have an increased risk of recurrence (19%).

3.8. Quality of life

As more people achieve long-term survival after penile cancer, sexual dysfunction and infertility are increasingly recognized as negative consequences affecting QoL.

A retrospective, face-to-face, structured interview study was carried out with Swedish patients treated with laser therapy for localized penile carcinoma during the period

Table 9 – Guidelines for follow-up in penile cancer

	Interval of follow-up		Examinations and Investigations	Maximum length of follow-up	GR
	Years 1 and 2	Years 3, 4 and 5			
Recommendations for follow-up of primary tumour					
Penile-preserving treatment	3 months	6 months	Regular physician or self-examination	5 years	C
Amputation	6 months	1 year	Regular physician or self-examination	5 years	C
Recommendations for follow-up of the inguinal lymph nodes					
'Wait-and-see'	3 months	6 months	Regular physician or self-examination Ultrasound with FNAB	5 years	C
pN0	6 months	1 year	Regular physician or self-examination Ultrasound with FNAB	5 years	C
pN+	3 months	6 months	Regular physician or self-examination Ultrasound with FNAB	5 years	C

GR = grade of recommendation; FNAB = fine-needle aspiration biopsy.

1986–2000 [63] (LE: 3). Some patients had delayed seeking treatment for a considerable period, despite awareness of the first local symptoms. Men with laser-treated localized penile carcinoma were able to resume their sexual activities to a large extent. Except for satisfaction with somatic health, a similar (or higher) proportion of patients were satisfied with life overall and with other domains, including sexual life.

Brazilian patients who underwent partial amputation answered the International Index of Erectile Function questionnaire to determine erectile function, orgasmic function, sexual desire, intercourse satisfaction,and overall satisfaction with sexual life [64]. The median patient age was 52 yr. The preoperative and postoperative scores were statistically worse for all domains of sexual function after partial penectomy.

4. Conclusions

Penile SCC of the penis is a severe, uncommon disease that is curable in 80% of cases in specialized centers. The disease is mainly related to poor hygiene, sexual history, and even smoking. The disease is facilitated by phimosis and may be preceded by chronic inflammations and condylomata. HPV infection is responsible for 40–50% of cases (sporalene and ultraviolet have different pathways).

The understanding of the natural history is fundamental, and it is very similar to that of SCC of the female genitalia, the horopharingx, and the anal canal. Globalization and promiscuity are expected to be the major causes of increasing SCC occurrences. The FDA licensed the first vaccine for HPV-6, -11, -16, and -18 for early prevention in young girls 11–12 yr old.

Early diagnosis can be performed by self and partner care, with the help of the family doctor. Early referral to specialized centers for correct diagnosis and staging is recommended; diagnosis, staging, and treatment of SCC of the penis need a multidisciplinary approach. The UK organization and multidisciplinary oncologic centers teach that understanding of the natural history, correct diagnosis and staging, selection of appropriate treatments, and appropriate follow-up are fundamental for the best oncologic results and QoL for penile cancer patents. The disclosure of so many diagnostics and treatments is a continuous study to improve knowledge, management, and long-standing results with the best possible QoL for the patients.

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Acquisition of data: Pizzocaro, Horenblas, Algaba, Tana, Van Der Poel, Solsona, Watkin.
Analysis and interpretation of data: Pizzocaro, Horenblas, Algaba, Tana, Van Der Poel, Solsona, Watkin.
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