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EAU Guidelines on Penile Cancer

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1. Background

Penile carcinoma is an uncommon malignant disease with an incidence ranging from 0.1 to 7.9 per 100,000 males. In Europe, the incidence is 0.1–0.9 and in the US, 0.7–0.9 per 100,000. In some areas, such as Asia, Africa and South America, penile carcinoma accounts for as many as 10–20% of male cancer.

Social and cultural habits seem to be important factors related to penile cancer, exemplified by the fact that 44–90% of patients suffer from phimosis at presentation and there is a documented association between human papilloma virus and penile carcinoma.

The localization of the primary tumor appears in the glans in 48% of cases, prepuce in 21%, both glans and prepuce in 9%, coronal sulcus in 6% and less than 2% in the shaft [1]. Palpable inguinal nodes are present at diagnosis in 58% of patients (range 20–96% [2]. Of these patients, 17–45% actually have nodal metastases [5]. The bilateral involvement is considerable due to the rich subcutaneous lymphatic communications of penis. Approximately 20% of patients with metastases to two or more nodes also have pelvic nodal involvement. Among patients with non-palpable nodes, around 20% harbor nodal micrometastases. Depth of invasion, tumor grade, vascular and lymphatic involvement and growth patterns and their associations are risk factors related to the occurrence of nodal metastases [3–6]. Molecular markers are currently under investigation as prognostic factors with no use in clinical practice.

An overall 5-year survival rate of 52% has been reported: 66% in patients with negative lymph nodes and 27% in patients with positive nodes [3,4,7,8].

2. Classification

2.1. Pathology

Squamous cell carcinoma is by far the most common malignant disease of the penis, accounting for more than 95% of cases.

2.1.1. Premalignant lesions

1. Lesions sporadically associated with squamous cell carcinoma of the penis: balanitis xerotica obliterans, cutaneous horn of the penis and Bowenoid papulosis of the penis.
2. Lesions at low risk of developing into squamous cell carcinoma of the penis: penile intraepithelial neoplasia (erythroplasia of Queyrat, Bowen's disease).

2.1.2. Penile neoplasias (squamous cell carcinoma)

1. Types: classic, basaloid, verrucous, sarcomatoid, adenosquamous.
2. Growth patterns: superficial spread, nodular or vertical-phase growth, verrucous.
3. Differentiation grades: the Broders [9] or the Maiche [10] system score (the most suitable).

2.1.3. Mesenchymal tumors (less than 3%)

Kaposi's sarcoma, angiosarcoma, epitheliod hemagioendothelioma, etc.

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Table 1
1997 TNM classification of penile cancer

Primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Non-invasive verrucous carcinoma
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra or prostate
T4	Tumor invades other adjacent structures
Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No evidence of lymph node metastasis
N1	Metastasis in a single inguinal lymph node
N2	Metastasis in multiple or bilateral superficial lymph nodes
N3	Metastasis in deep inguinal or pelvic lymph nodes unilateral or bilateral
Distant metastasis	
Mx	Distant metastases cannot be assessed
M0	No evidence of distant metastases
M1	Distant metastases

2.1.4. Metastatic disease (uncommon)

Prostate, rectal tumors are reported as primary tumors in cases of metastatic disease.

2.2. Tumor, nodes, metastasis (TNM) classification

The 1997 TNM classification for penile cancer is shown in Table 1.

3. Guidelines on diagnosis of penile cancer

In order to establish a rational diagnostic approach to penile cancer, the primary lesion, regional lymph nodes and distant metastases should be taken into account initially and during follow-up. Patients with a suspicious penile lesion should undergo a detailed physical examination on primary tumor as well as inguinal regions in order to determine the presence or absence of palpable nodes. In this examination, to record diameter, location, number, morphology, color, boundaries, mobile or fixed of lesions and relationship of the primary tumor or/and palpable nodes with other structures is a mandatory recommendation. Cytological or histological diagnosis of both primary tumor or palpable nodes is absolutely necessary for making treatment decisions.

Diagnostic imaging can assist in identifying the depth of tumor invasion, particularly with regard to corpora cavernosa infiltration. However, penile ultrasound imaging is sometimes difficult to interpret and is an unreliable method with microscopic infiltration [11]. MRI is an optional method if ultrasound is inconclusive.

An assessment of distant metastases should only be performed in patients with proven positive nodes [3].

A diagnostic schedule for penile cancer is shown in Table 2.

4. Guidelines on treatment of penile carcinoma

There are still many controversies regarding the management of penile cancer. Treatment of the primary tumor tends to be organ preserving in order to maintain sexual function [12]. Another point of debate relates to the need and extent of lymphadenectomy in clinically node negative patients.

In penile carcinoma, the success of therapy is related to lymph node status and treatment. Lymphadenectomy has been shown to be an effective therapy for

Table 2
Diagnosis schedule for penile cancer

Lesion level	Procedures		
	Mandatory	Advisable	Optional
Primary tumor	Physical examination Cytological or histological diagnosis	Ultrasound (if invasion suspected)	MRI (if ultrasound inconclusive)
Regional disease			
Non-palpable nodes	Physical examination		Sentinel node biopsy (investigational)[a]
Palpable nodes	Cytological or histological diagnosis		
Distant metastases		Pelvic CT (if nodes +ve) Abdominal CT (if pelvic nodes +ve) Chest X-ray (if nodes +ve)	Bone scan (in symptomatic patients)

MRI: magnetic resonance imaging.
[a] Cabañas technique is no longer advisable. Isosulfan blue or 99m Tc-colloid sulfur are promising new investigational procedures.

patients with positive lymph nodes [3,7,8]. However, this procedure is associated with a high morbidity rate of 30–50% [3,7,8], even with modern technical modifications [13]. This morbidity precludes its prophylactic use, although some controversy still surrounds this aspect [8,14]. A rational use of lymphadenectomy requires a careful groin assessment and awareness of predictive factors for positive lymph nodes [3–6,15]. In this sense, in patients with non-palpable nodes three risk groups of patients can be defined using pathological predictive factors from primary tumor: *low risk*, including patients with categories pTis, pTaG1-2 or pT1G1; *high risk*, including categories pT $\geq$ 2 or G3 tumors, and *intermediate risk*; including categories pT1G2. According to these risk groups, a surveillance is recommended in low risk, a lymphadenectomy (LND) in high risk and in intermediate risk the decision-making process might be based on the presence of vascular or lymphatic invasion and growth pattern.

Other general recommendations include performing: a ''modified'' LND in patients with non-palpable nodes and it can be enlarged to a radical LND if positive nodes are present. Bilateral radical inguinal LND is the standard recommendation in cases of positive nodes but pelvic LND could be performed in cases of $\geq$2 positive inguinal nodes or extracapsular invasion. These patients also are good candidates for adjuvant chemotherapy. When inguinal palpable nodes appear after a surveillance program a radical inguinal LND at the site of positive nodes according to the disease-free interval can be an option to bilateral LND. Patients with fixed inguinal masses or clinically positive pelvic nodes (CT or MRI) are good candidates to induction chemotherapy followed by radical ilio-inguinal LND. In these patients, another strategy is to use pre-operative radiotherapy but with harmful complications.

A therapeutic schedule for penile cancer is shown in Table 3.

4.1. Integrated therapy

In patients presenting with a primary tumor together with positive nodes, both problems should be managed simultaneously. In patients presenting initially with positive pelvic nodes, induction chemotherapy could be administered first and radical or palliative surgery or

Table 3
Therapeutic schedule for penile cancer

Lesion level	Therapy	Recommendations		
		Strong	Optional	Investigational
Primary tumor	Conservative therapy	Primary/recurrent Tis, Ta-1G1-2	T1G3, T $\geq$ 2 (fit patients for surveillance with <0.5 glans)	After chemotherapy in patients unfit for conservative therapy
	Total/partial amputation	Primary/recurrent T1G3, T $\geq$ 2	Primary or recurrent Ta-1G1-2 (conservative therapy not feasible)	
Regional (non-palpable nodes)	Surveillance	Tis, TaG1-2, T1G1, T1G2 Superficial growth, vascular (−)	T2G2-3 (preference and fit patients for follow-up)	Negative sentinel node
	Modified LND[a]	T1G2 nodular growth or vascular (+), T1G3 or any T2	T1G2 vascular (−) flat growth (unfit patients for follow-up)	Positive sentinel node
Regional (palpable nodes)	Radical LND[b]	Positive nodes at presentation	Plus adjuvant chemotherapy[c] or radiotherapy[d] (>1 positive node)	
		Positive nodes after surveillance	Unilateral LND on nodal site (disease-free interval >3–6 months)	
	Chemotherapy[c] ± LND	Fixed inguinal masses, >2 cm pelvic nodes (fit patients for chemotherapy)		
	Radiotherapy[d] ± LND		Fixed masses (unfit patients for chemotherapy)	
Distant metastases			Chemotherapy[c] or palliative therapy (according to performance status, age, etc.)	

LND: lymphadenectomy.
[a] Modified LND can be extended to radical in cases where there are positive nodes.
[b] If unilateral non-palpable nodes on the opposite side, modified LND can be carried out. Pelvic LND for more than one positive inguinal node only.
[c] Chemotherapy should be discussed with medical oncologist and preferably be given in the context of clinical trials.
[d] Radiotherapy has inconsistent results and high morbidity associated with surgery.

radiotherapy when indicated according to the tumor response.

4.2. Distant metastases

This approach is only recommended optionally in selected cases where prolonging survival may be important or in symptomatic patients with good performance status and in combination with palliative procedures.

4.3. Quality of life

Patients' age, performance status, socio-economic status, sexual function, patient motivation and morbidity of different procedures should be considered in the decision-making process.

4.4. Technical aspects

- With the primary lesion, the simplicity and morbidity of the procedure and surgeon's experience play a more important role in the choice of conservative strategy than anything else. Formal circumcision should be advised before brachytherapy.
- Partial amputation does not require removal of 2 cm of the penis in order to achieve macroscopically free margins. Although this is probably more then necessary, it is essential to achieve negative margins with pathological confirmation.
- Radical inguinal lymphadenectomy should include the following anatomical landmarks: inguinal ligament, adductor muscle, sartorius muscle with the femoral vein and artery as the floor of dissection.
- 'Modified' inguinal lymphadenectomy, implies preservation of the saphenous vein and 1–2 cm reduction of external and inferior boundaries.
- Pelvic lymphadenectomy includes the external iliac lymphatic chain and the ilio-obturator chain.

4.5. Chemotherapy

The chemotherapy regimen should be discussed with the medical oncologist. However, the following can be used as guidelines.

- Induction chemotherapy: three to four courses of cisplatin and 5-fluor-uraci with appropriate doses and sequence [16].
- Adjuvant chemotherapy: two courses of cisplatin and 5-fluor-uracil may be sufficient or 12 weekly courses of vincristine, methotrexate and bleomycin may be administered on an outpatient basis [17].

5. Guidelines for follow-up in penile cancer

Penile carcinoma is one of the few solid tumors in which lymphadenectomy can provide a high cure rate even if lymphnode are involved. Urologists are faced with the dilemma of reaching an appropriate balance between decreasing the morbidity with conservative procedures and disease control. In this context, follow-up is crucial in order to achieve similar survival rates with early or delayed lymphadenectomy. Moreover, although most relapses occur during the first 2 years, late recurrences, although uncommon, can be present [18]. Penile carcinoma is associated with poor social-economical condition, thus a close surveillance cannot always be performed.

With respect to the primary lesion, the local disease recurrence rate with partial or total penectomy ranges from 0% to 7% [19]; with conservative therapies, this

Table 4
Follow-up schedule for penile cancer

Lesion level	Therapy	Interval			Examinations	
		Years 1 and 2	Year 3	Years 4 and 5	Mandatory	Advisable
Primary tumor	Conservative therapy	2 months	3 months	6 months	Physical/self exam/QOL	
	Partial/total penectomy	4 months	6 months	Yearly	Physical/self exam/QOL	
Regional approach	Surveillance	2 months	3 months	6 months	Physical exam/QOL	Cytology or biopsy if unclear clinical findings
	LND (pN0)	4 months	6 months	Not necessary	Physical/self exam/QOL	
	LND (pN+)	Institutional protocol[a]	Institutional protocol[a]	Institutional protocol[a]	Physical/self exam/QOL/CT scan/chest X-ray	Bone scan (symptoms)

LND: lymphadenectomy; QOL: quality of life (physical and sexual); CT: computed tomography.
[a] Based on the therapeutic approach applied. It is advisable, however, to carry out follow-up every 2–3 months for 2 years, then every 4–6 months during the third year and every 6–12 months thereafter.

might increase to 50% [19–22]. Nevertheless, local disease recurrence does not have a negative impact on cause-specific survival, provided early diagnosis is carried out [23].

As penile and inguinal lymph nodes are externally situated, follow-up in patients with penile carcinoma is based essentially on inspection and physical evaluation. In patients with initially palpable inguinal nodes, the reliability of physical evaluation with respect to pathological examination ranges from 47% to 86% [3,5]. Moreover, in cases of initially non-palpable lymph nodes, the development of palpable nodes upon physical evaluation represents a reliability close to 100% after pathological examination.

The follow-up interval and strategies for patients with penile cancer are directly related to the initial treatment of the primary lesion and regional lymph nodes.

A follow-up schedule for penile cancer is shown in Table 4.

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