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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 (1). In some areas, such as Asia, Africa and South America, penile carcinoma accounts for as many as 10% to 20% of male cancer. Phimosis and chronic irritation processes related to poor hygiene are commonly associated with this tumour, whereas neonatal circumcision gives a protection against the disease. There is strong evidence that human papilloma virus types 16 and 18 are associated with penile carcinoma in as many as 50% of cases, as well as to penile carcinoma in situ (2)

Penile carcinoma essentially metastasises via the lymphatics and mainly through the embolization mechanism instead of lymphatic permeation. Distant metastases are very rare and are a result of vascular dissemination (3). Spreading essentially develops in stepwise fashion: first inguinal lymphatic spread, followed by pelvic and lastly distant metastases. As a consequence, it is extremely rare to observe patients with positive pelvic nodes or distant metastasis without inguinal lymph-node involvement. The localisation of the primary tumour may appear 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 (4). Palpable inguinal nodes are present at diagnosis in 58% of patients (range 20-96%) (4). Of these patients, 17-45% actually have nodal metastases and the remaining patients will have inflammatory disease secondary to infection of primary tumour. The possibility of bilateral involvement is considerable due to the rich communications of penile lymphatics in the subcutaneous tissue. Approximately 20% of patients with metastases to two or more nodes also have pelvic nodal involvement (5). Among patients with non-palpable nodes, around 20% harbour nodal micrometastases. Depth of invasion, tumour grade, vascular and lymphatic involvement and growth pattern and their associations are related to the occurrence of nodal metastases (6-10).

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 (4,5,7,11,12). Most patients are elderly and the neoplasm has a slow growth rate. Death from cancer is usually a consequence of local complications such as infection, haemorrhage of the ulcerated tumour or ulcerated inguinal metastases.

There are still many controversies regarding management of penile cancer. Treatment of the primary tumour tends to be more organ preserving in order to maintain sexual function (13). Another point of debate relates to the need and extent of lymphadenectomy in clinically node negative patients. Also, 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 (3) and there is a documented association between human papilloma virus and penile carcinoma (2).

All these factors, together with the low incidence rate in countries with high socio-economic conditions and the absence of large or randomised trials, have an important influence in management of the disease.

2. CLASSIFICATION

Pathology

Squamous cell carcinoma is by far the most common malignant disease of the penis, accounting for more than 95% of cases. Malignant melanomas and basal cell carcinoma are less common. To what extent squamous cell carcinoma is preceded by pre-malignant lesions is unknown.

Premalignant lesions

Premalignant lesions of squamous cell carcinoma of the penis include the following:

1. Lesions sporadically associated with squamous cell carcinoma of the penis (14):
    - Balanitis xerotica obliterans
    - Cutaneous horn of the penis
    - Bowenoid papulosis of the penis.
2. Lesions at low risk of developing squamous cell carcinoma of the penis (up to one-third of transformation to invasive squamous cell carcinoma has been reported [15]):
    - Penile intraepithelial neoplasia (Erythroplasia of Queyrat, Bowen's disease.

Penile neoplasias

Although squamous-cell carcinoma is the most common form of penile cancer, various types of this entity and different growth patterns can be observed:

1. Squamous cell carcinoma types:
    - Classic type
    - Basaloid
    - Verrucous
    - Sarcomatoid
    - Adenosquamous.
2. Squamous cell carcinoma growth pattern:
    - Superficial spread
    - Nodular or vertical-phase growth
    - Verrucous.
3. Differentiation grades: the Broders system (16) has been traditionally used as a grading system but currently, the Maiche system score (17) seems to be the most suitable.

Mesenchymal tumours

Mesenchymal tumours are very uncommon with an incidence rate of less than 3% (Kaposi's sarcoma, angiosarcoma, epitheliod hemagioendothelioma, etc.).

Metastatic disease

The penis is a very rare metastatic site, but bladder, prostate, rectal tumours are reported as primary tumours in cases of metastatic disease.

TNM

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

3. RISK FACTORS

The best prognostic factors related to survival are the presence of positive lymph-nodes, the number of positive nodes and the extracapsular nodal involvement (1,2). Therefore, these are important factors in order to apply complementary therapies after pathological examination. Related to the prognostic value of the lymph-node condition, predictive factors for the presence of lymph-node have been assessed thoroughly. Parameters from primary tumour, location, size, depth of infiltration, tumour grade (3,4,5,6,7) and their association (7) have shown an important predictive value. According to these factors high, intermediate and low risk groups of patients have been defined (4,7,8). Vascular, lymphatic invasion and the growth pattern of primary tumour (9,10) should be other important predictive factors with particular relevance in the intermediate risk group. All these factors have been taken into account when therapy recommendations have been outlined.

Molecular markers are currently under investigation as prognostic factors with no use in clinical practice.

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4. DIAGNOSIS

In order to establish a rational diagnostic approach, the primary lesion, regional lymph nodes and distant metastases should be taken into account initially and during the follow-up.

Primary lesion

Patients with a suspicious penile lesion should undergo a physical examination. This is a very important aspect, as it is often sufficient for diagnosis and staging, as well as for therapeutic decision making.
It is important to record:

- Diameter of penile lesion or suspicious areas
- Penile location(s)
- Number of lesions
- Morphology, papillary, nodal-ulcer or flat
- Relationship with other structures (submucosa, corpora spongiosa and/or cavernosa, urethra, etc)
- Colour and boundaries.

Cytology or histological diagnosis is absolutely necessary in treatment decisions. The aim is not only to confirm the pathological diagnosis, but also to determine the tumour grade. This will assist in primary tumour therapeutic decisions, as well as establishing risk groups for regional therapeutic strategy (8). The preference of the pathologist should be taken into account when deciding the most suitable histological diagnostic method. The pathological diagnosis can be made by incisional biopsy, tissue core biopsy, fine needle aspiration, or brush biopsy (like cervical cancer). Excisional biopsy can also be used as a conservative approach if a small lesion is located in the prepuce or in another feasible area.

Imaging diagnosis can assist in identifying the depth of tumour 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 (18). Magnetic resonance imaging (MRI) is an optional method if ultrasound is inconclusive. However, there is limited experience with this method (19).

Regional nodes

A careful inguinal physical examination is necessary, taking into account the following aspects.

Non-palpable nodes

There is no indication for imaging or histological examination if the nodes are non-palpable. If poor prognostic factors were observed on primary tumour, a pathological surgical inguinal nodal staging is advised (see later). Nevertheless, biopsy of the sentinel node, as described by Cabañas (20), is not recommended, because false negative rates as high as 25% (range 9-50 %) have been reported (21). More recently, a dynamic sentinel lymph node biopsy with isosulfan blue and/or 99m Tc-colloid sulfur is a promising procedure under investigation (22,23).

Palpable nodes
The following parameters should be recorded if palpable nodes are present:

- Diameter of node(s) or mass(es)
- Uni- or bilateral localization
- Number of nodes identified in each inguinal area
- Mobile or fixed nodes or mass
- Relationship to other structures (skin, Cooper ligament, etc.) with respect to infiltration, perforation, etc.
- Presence of oedema on leg and/or scrotum.

The histological diagnosis involves fine needle aspiration biopsy, tissue core biopsy, or open biopsy according to the preference of the pathologist. In the case of a negative biopsy and clinically suspicious nodes, a repeat biopsy or excisional biopsy should be performed.

Distant metastases

An assessment of distant metastases should only be performed in patients with proven positive nodes (24,25). Pelvic/abdominal CT scan is used in the identification of pelvic and/or retroperitoneal nodes in patients with inguinal metastases. Although this is not a reliable diagnostic method (26), the detection of pelvic masses impacts on therapy and prognosis considerably (27,28). A chest x-ray should be performed on patients with positive lymph nodes. Routine blood determinations should be done only on patients with bulky inguinal masses and pelvis nodes, and in metastatic patients (29,30). A bone scan is recommended only in symptomatic cases (24).
A diagnostic schedule is summarised in Table 2.

GUIDELINES ON DIAGNOSIS OF PENILE CANCER

Primary tumour

1. Physical examination is mandatory, recording morphological and characteristics of physical lesion.
2. Cytological or histological diagnosis is also a mandatory recommendation.
3. Imaging: penile ultrasound is an advisable recommendation to demonstrate corpora cavernosa invasion. In cases of inconclusive results, MRI is an optional method.

Regional lymph nodes

1. Physical examination is a mandatory evaluation:
    - If nodes non-palpable, there is no indication for imaging or histological examination. A new technique - sentinel node biopsy - is investigational in high-risk patients.
    - IIf nodes palpable, it is mandatory to record nodal morphological and physical characteristics and perform a histological diagnosis.

Distant metastasis (only in patients with metastatic inguinal nodes)

1. Pelvic/abdominal CT scan (positive pelvic nodes) is an advisable recommendation.
2. Chest x-ray is also an advisable recommendation.
3. Routine laboratory determinations are recommended as optional for specific conditions.
4. Bone scan is only recommended in symptomatic cases.

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5. TREATMENT

Primary lesion

Penile intraepithelial neoplasia

In cases of penile intraepithelial neoplasia, a penis preserving strategy is strongly recommended. The following therapies have been used successfully: laser therapy (CO2-laser or Nd-YAG), cryotherapy, local excision and Mohs' surgery. The therapeutic approach should be decided according to the preference of the surgeon and available technology.

Category Ta-1G1-2

For patients who can guarantee a regular follow-up, a penis preserving strategy (laser therapy, local excision plus reconstructive surgery, brachytherapy) is strongly recommended. A pathological assessment of surgical margins is essential in applying these procedures (1). Local recurrence rate ranges between 12-17% (1-4). Meticulous follow-up is essential in order to treat local recurrences as soon as possible. In patients who do not comply with regular follow-up, partial amputation is an optional recommendation.

Category T1G3, T≥2

Partial or total amputation or emasculation according to tumour extent can be considered as standard therapies (5-7). A conservative strategy is an alternative in very selected patients with tumours encompassing less than half of the glans in whom a close follow-up can be carried out (8). Chemotherapy induction courses within the context of a clinical trial, followed by conservative procedures in cases of complete or partial response, can be considered an investigational recommendation. Promising results have been reported with the latter procedure, even in cases of corpora cavernosa infiltration (9).

Local recurrence

For local recurrence after conservative therapy, a second conservative procedure is strongly advised if no corpora cavernosa invasion is present (10). However, if there is a large or a deep infiltrating recurrence, a partial or total amputation is strongly recommended.

Regional nodes

In penile carcinoma, the success of therapy is related to lymph-node status and treatment. For patients with positive lymph nodes, lymphadenectomy has been shown to be an effective therapy (11-13). However, this procedure is associated with a high morbidity rate of 30-50% (14), even with modern technical modifications (15,16). This morbidity precludes its prophylactic use, although some controversy still exits on this aspect (17,18). A rational use of lymphadenectomy implies a careful groin assessment and being aware of predictive factors for positive lymph nodes (11,19-21).

Non-palpable nodes

In patients at low risk of nodal micrometastases (pTis, pTaG1-2 or pT1G1), a surveillance programme is strongly advised, as the probability of occult micrometastases in inguinal lymph-nodes is less than 16.5% (19,22,23). If patients are considered unfit for surveillance a 'modified' inguinal lymphadenectomy is suggested as an optional recommendation.

In cases of intermediate risk (T1G2), vascular or lymphatic invasion and growth pattern can be taken into account before therapeutic decision making (19-24). In patients with no vascular or lymphatic invasion, or superficial growth pattern on primary tumour, a surveillance programme is a mandatory recommendation. However, a modified lymphadenectomy is strongly recommended in cases of vascular or lymphatic involvement or infiltrating growth pattern, unless patients are reliable for a regular follow-up.

In patients at high risk of nodal involvement (T≥2 or G3), modified or radical inguinal lymphadenectomy

can be strongly recommended. In these patients, the incidence of occult metastases ranges between 68% and 73% (19,22-24).
A 'modified' lymphadenectomy can be extended to a radical lymphadenectomy if positive nodes are present on frozen sections. A sentinel lymph node biopsy with Isosulfan blue and/or 99m Tc-colloid sulfur should be considered before undertaking a lymphadenectomy as an investigational procedure (25,26).

Palpable nodes with positive histopathology
Bilateral radical inguinal lymphadenectomy is strongly recommended for palpable nodes. Great controversy exists about when to perform pelvic lymphadenectomy, as only a few patients with positive pelvic nodes have been rescued with this approach (27,28). Immediate or delayed pelvic lymphadenectomy could be performed in cases of two or more positive inguinal lymph-nodes or extracapsular invasion found on frozen sections biopsies or standard pathology exam. In these cases, the incidence of positive pelvic nodes increases up to 30% (27) and often microscopic metastases offer some chance for cure. On contralateral inguinal area with no palpable nodes, a modified lymphadenectomy can initially be considered and it enlarged if positive nodes are present in frozen section biopsies.

For patients with fixed inguinal masses or clinically positive pelvic nodes (CT scan or MRI), induction courses of chemotherapy followed by radical ilio-inguinal lymphadenectomy when complete or partial response is reached is strongly recommended (29). With systemic chemotherapy, a partial or complete clinical response can be achieved in 21-60% of cases (30-34). It is suggested that this strategy be adopted within the context of clinical trials. Another strategy is to use pre-operative radiotherapy (35), but the increased morbidity of lymphadenectomy after radiotherapy should be taken into account. Nevertheless, this approach is known to be beneficial with other types of cancer, e.g. rectal and squamous cell carcinoma of head and neck regions.

When inguinal palpable nodes appear after a surveillance programme, two strong recommendations are made:
- Bilateral radical inguinal lymphadenectomy following similar criteria to that discusses above
- Inguinal lymphadenectomy, performed at the site of positive nodes in the case of a long disease-free interval. The development of positive nodes after surveillance should appear synchronously or with a very short interval in both inguinal areas. Thus, the probability of developing subsequent late lymph-node metastases in contralateral inguinal area after initial unilateral inguinal lymph-node recurrence is around 10% (36). Therefore, unilateral lymphadenectomy could be warranted in these cases, but a follow-up programme is advised.

Adjuvant therapy is advised when there are two or more positive nodes or extracapsular nodal involvement on pathological exam, as the prognosis of these patients is poorer than in patients with a single positive lymph node (22,37). Even though random trials are not available, phase II trials suggest that adjuvant chemotherapy is beneficial for these patients (38), but these adjuvant programmes should be performed within controlled clinical trial. Fewer data are available on adjuvant radiotherapy (35).

GUIDELINES ON TREATMENT OF PENILE CARCINOMA

Recommendations for therapy of primary lesion
1. Penile intraepithelial neoplasia: penis preserving strategy is strongly recommended
2. Category Ta-1G1-2: penis conservative strategy is strongly recommended. In patients who do not comply with regular follow-up, partial amputation is an optional alternative.
3. Category T1G3, T≥2: partial or total amputation or emasculation according to tumour extent can be considered as standard therapy. Conservative therapies in very selected patients. Chemotherapy followed by conservative procedures is an investigational option.
4. If local recurrence develops after conservative therapy, a second conservative procedure is strongly advised if no corpora cavernosa invasion. If large or infiltrating recurrence, a partial or total amputation is also strongly recommended.

Recommendation for regional nodes therapy if non palpable nodes
1. In patients at low risk of occult metastases (pTis, pTaG1-2 or pT1G1), a surveillance program is strongly advised. Patients considered unfit for surveillance a modified lymphadenectomy (LND) is an optional recommendation
2. In patients at high risk (pT≥2 or G3), modified or radical LND is strongly recommended.
3. In cases of intermediate risk (pT1G2), vascular or lymphatic invasion and growth pattern can be considered for a therapeutic decision. A strict surveillance could be an option in patients suitable for a reliable regular follow-up.

4. “Modified” LND can be enlarged to a radical LND if positive nodes are present.
5. A sentinel lymph node biopsy with Isosulfan blue or/and 99m Tc-cloide sulfur should be considered as an investigational procedure.

Recommendations for regional node therapy if palpable pathological positive nodes

1. Bilateral radical inguinal LND is the standard recommendation. Pelvic LND could be performed in cases of ≥2 positive inguinal nodes or extracapsular invasion. A modified LND can initially be considered on contralateral inguinal area with no palpable nodes.
2. 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. Another strategy is to use pre-operative radiotherapy but with harmful complications.
3. When inguinal palpable nodes appear after a surveillance program, we have two possible recommendations: a) bilateral radical inguinal LND or b) inguinal LND at the site of positive nodes according to the disease-free interval
4. Adjuvant chemotherapy is advisable recommendation when there are ≥2 positive nodes or extracapsular nodal involvement. Another option is adjuvant radiotherapy

Integrated therapy

In patients presenting with a primary tumour together with positive nodes, both problems should be managed simultaneously. In patients presenting initially with positive pelvic nodes, induction chemotherapy could be administered firstly and radical or palliative surgery or radiotherapy could be indicated according to the tumour response.

Distant metastases

Chemotherapy courses or palliative therapy can be tried according to age, performance status and patient preference. Because of the poor efficacy of chemotherapy in metastatic disease, this approach is only optionally recommended in selected cases where prolonging survival can be important or in symptomatic patients with good performance status in combination with palliative procedures.

Quality of life

With regard to quality of life, age, performance status, socio-economic context, sexual function, patient motivation and morbidity of different procedures should be considered in the decision-making process. Other important factors to regard before therapeutic decision making are psychological condition, economic status, geography and tumour biology, since penile carcinoma is a malignant disease with a high probability of cure, but with high therapeutic morbidity.

Technical aspects

- With the primary lesion, simplicity, morbidity and experience play a more important role in the choice of conservative strategy than anything else. A formal circumcision should be advised before brachytherapy.
- Partial amputation traditionally required removal of 2 cm in order to achieve macroscopically free margins. However, this is probably more than necessary, but the aim must always be to have free tumour margins with pathological confirmation.
- Radical inguinal lymphadenectomy should include the following anatomic landmarks: inguinal ligament, adductor muscle, sartorius muscle with the femoral vein and artery as floor of dissection.
- ‘Modified’ inguinal lymphadenectomy, implies the saphenous vein preservation and 1-2 cm lateral boundaries reduction on external and inferior boundaries. With these modifications, complications and morbidity rates are lower than radical ilio-inguinal lymphadenectomy.
- Pelvic lymphadenectomy includes external iliac lymphatic chain and ilio-obturator chain (proximal boundary: iliac bifurcation, lateral: ilio-inguinal nerve).

Chemotherapy

Chemotherapy regimen should be discussed with the medical oncologist. However, the following can be used as guideline:

- Induction chemotherapy: three to four courses of cisplatin and 5-fluoruracil with appropriate doses and sequence.
- Adjuvant chemotherapy: two courses of cisplatin and 5-fluoruracili may be sufficient or 12 weekly courses of vincristin, methotrexate and bleomycin administered on an outpatient basis (38).

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

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6. FOLLOW-UP

Penile carcinoma is one of the few solid tumours in which lymphadenectomy can provided a high cure rate even if lymph-nodes are involved. This is related to its particular biology, as the disease essentially develops in a stepwise fashion. However, penectomy and inguinal node dissection are associated with important morbidity. Urologists are faced, therefore, with the dilemma of reaching an appropriate balance between decreasing the morbidity with conservative procedures and disease control. In this context, the follow-up is crucial in order to achieve similar survival rates. Moreover, most relapses occur during the first 2 years and late recurrences, although uncommon, can be present. Penile carcinoma is associated with poor social-economical condition, thus a close surveillance cannot always be performed.

Why follow-up?

With respect to the primary lesion, the local recurrence rate is extremely variable according to the type of therapy carried out. With partial or total penectomy, the incidence of local recurrence ranges from 0% to 7% (1,2); with conservative therapies, this might increase to 50% (2-5). Nevertheless, local recurrence does not have a negative impact on cause-specific survival, provided an early diagnosis is carried out (6).

Controversy between early and delayed lymphadenectomy in patients with initial non-palpable inguinal lymph-nodes still remains. Some authors achieve similar survival rates with both approaches (5,7). However, a surveillance programme implies a close follow-up, since late diagnosis seems to be a negative prognostic factor.

In summary, the potential development of local recurrence and inguinal lymph nodes in patients treated with conservative approaches and the possibility of rescuing patients with an early detection justify the need of a follow-up in patients with penile carcinoma.

How to follow-up?

Since penile and inguinal lymph nodes are external areas, the follow-up in patients with penile carcinoma is essentially based on inspection and physical evaluation. In patients with initially palpable inguinal nodes, the reliability of physical evaluation with respect to pathological examination ranges from 47-86% (8,9). Moreover, in cases of initially non-palpable lymph nodes, the development of palpable nodes upon physical evaluation represents a reliability close to 100%.

CT scan and chest x-rays can be additional tests in order to identify pelvic lymph nodes or distant metastases in specific circumstances, since the tumour mainly spreads in these areas. Other diagnostic tests should be use on in symptomatic patients.

When to follow-up?

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

Primary tumour

If the primary lesion was treated with conservative therapy (local resection, laser therapy, brachytherapy, Mohs' procedure, associated therapies), a follow-up interval of 2 months for 2 years and then every 3 months for a further year is recommended, because most of the local recurrences occur in this period. Nevertheless, a long-term follow-up is also recommended every 6 months due to the fact that late local recurrences have been observed (10). Patient self-evaluation is also advisable and patients should be informed about the possible warning signals. This follow-up schedule is advised because the recurrence rate is high and the probability of rescuing patients is also elevated.

If patients were treated with partial or total penectomy, a follow-up every 4 months for 2 years, then 6-monthly intervals for 3 more years and thereafter yearly is recommended. For this last period, no hard data are available to suggest a specific interval. This schedule is recommended because local recurrence, although infrequent, usually occurs very early and because of the aggressive behaviour of the tumour (6), an early diagnosis is necessary.

Regional areas

If a surveillance programme was decided after the primary tumour was removed, a groin evaluation every 2 months for 2 years, then every 3 months during the next year and every 6 months for a further 2 years is recommended. No CT scan and chest x-rays are necessary. The rational for this scheme is based on the fact that most of the inguinal lymph node recurrences are detected during the first 2 years. Moreover, when recurrences develop their growth is very quick and the prognosis is related to number, size and bilaterality of the lymph nodes (11,12). A very close follow-up is therefore advisable.

If an inguinal lymphadenectomy was performed and no tumour was found on pathological examination of the specimen, a physical evaluation is recommended every 4 months for 2 years and every 6 months for the next year; subsequently, it is not completely necessary to do a follow-up. In these cases, a local or distant relapse is rare if a radical procedure and extensive pathological examination have been performed. The follow-up is focused essentially on the quality of life for these patients, since the inguinal lymphadenectomy has a high morbidity rate.

If an inguinal lymphadenectomy was performed and positive lymph nodes were observed on pathological examination, a specific follow-up cannot be recommended, since many variables should be taken into account, including:

- Number of positive lymph nodes (uni- or bilaterality)
- Pelvic lymphadenectomy performed, with or without positive lymph nodes
- Adjuvant radiotherapy carried out and what scheme.

In relation to these variables, physical examination, CT scan, chest x-ray and the appropriate intervals should be defined by each institution.

Bone scan and other tests are only recommended in symptomatic patients. Quality of life assessment should essentially encompass sexual activity and lymphadenectomy morbidity (lymphoedema).
The follow-up schedule is summarized in Table 4.

GUIDELINES FOR FOLLOW-UP IN PENILE CANCER

Primary tumour

1. Patients treated with conservative therapies: follow-up every 2 months for 2 years, every 3 months for 1 more year; long-term follow-up also recommended every 6 months. Physical and self-examination should be performed.
2. Patients treated with partial or total penectomy: follow-up every 4 months for 2 years, twice during the third year and then each year thereafter is recommended.

Regional nodes and distant metastasis

1. If a surveillance programme was decided after the primary tumour was removed, a groin evaluation every 2 months for 2 years, then every 3 months for 1 more year and every 6 months for the next 2 years is recommended.
2. If an inguinal lymphadenectomy was performed (pN0), physical evaluation is recommended every 4 months for 2 years, then every 3 months for 1 more year and afterwards it is not completely necessary to do a follow-up.
3. If an inguinal lymphadenectomy was performed (pN1-3) a specific follow-up cannot be recommended. Physical examination, CT scan, chest x-ray and the appropriate intervals should be defined by each institution.
4. Bone scan and other tests are only recommended in symptomatic patients.

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Table 1: 1997 TNM classification of penile cancer

Primary tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
Ta	Non invasive verrucous carcinoma
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades corpus spongiosum or cavernosum
T3	Tumour invades urethra or prostate
T4	Tumour 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

Table 2: Diagnosis schedule for penile cancer

	Procedures		
Lesion level	**Mandatory**	**Advisable**	**Optional**
Primary tumour	Physical examination Cytological or histological diagnosis	Ultrasound (if invasion suspected)	MRI (if ultrasound inconclusive)
Regional disease Non-palpable nodes Palpable nodes	Physical examination Cytological or histological diagnosis		Sentinel node biopsy[1] (investigational)
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.

[1] Cabañas technique is no longer advisable. Isosulfan blue or 99m Tc-colloid sulfur are promising new investigational procedures.

Table 3: Therapeutic schedule for penile cancer
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Lesion level	Therapy	Recommendations		
		Strong	**Optional**	**Investigational**
Primary tumour	Conservative therapy	Primary/recurrent Tis, Ta-1G1-2	T1G3, T ≥ 2 (fit patients for surveillance with < 0.5 glans)	After chemotherapy in patients Unfit for conservative therapy
	Total/partial amputation	Primary/recurrent T1G3, T ≥ 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[1]	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[2]	Positive nodes at presentation Positive nodes after surveillance	Plus adjuvant chemotherapy3 or radiotherapy4 (> 1 positive node) Unilateral LND on nodal site (disease-free interval > 3-6 months)	
	Chemotherapy +/- LND[3]	Fixed inguinal masses > 2 cm pelvic nodes (fit patients for chemotherapy)		
	Radiotherapy[4] +/- LND		Fixed masses (unfit patients for chemotherapy)	
Distant metastases			Chemotherapy3 or palliative therapy (according to performance status, age, etc.)	

LND = lymphadenectomy.

1 Modified LND can be enlarged to radical in cases of positive nodes.

2 If unilateral non-palpable nodes on the opposite side, a modified LND can be done. Pelvic LND for more than one positive inguinal node only.

3 Chemotherapy should be discussed with medical oncologist and preferably in clinical trials.

4 Radiotherapy has inconsistent results and high morbidity associated with surgery.

Table 4: Follow-up schedule for penile cancer

		Interval			Examinations	
Lesion level	**Therapy**	**Years 1 and 2**	**Year 3**	**Years 4 and 5**	**Mandatory**	**Advisable**
Primary tumour	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[1]	Institutional protocol[1]	Institutional protocol[1]	Physical/self exam/QOL/CT scan/chest x-ray	Bone scan (symptoms)

LND = lymphadenectomy; QOL = quality of life (physical and sexual).

1 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.

SUMMARY OF GUIDELINES ON TREATMENT OF PRIMARY PENILE TUMOUR

1. Penile intraepithelial neoplasia: penis preserving strategy is strongly recommended
2. Category Ta-1G1-2: penis conservative strategy is strongly recommended. In patients who do not comply with regular follow-up, partial amputation is an optional alternative.
3. Category T1G3, T≥2: partial or total amputation or emasculation according to tumour extent can be considered as standard therapy. Conservative therapies in very selected patients with tumours less than half of the glans is an optional recommendation. Chemotherapy followed by conservative procedures can be considered as an investigational recommendation.
4. If local recurrence develops after conservative therapy, a second conservative procedure is strongly advised if no corpora cavernosa invasion. If large or infiltrating recurrence, a partial or total amputation is also strongly recommended.

SUMMARY OF GUIDELINES ON TREATMENT OF REGIONAL LYMPH NODES IF NON-PALPABLE

1. In patients at low risk of occult metastases (pTis, pTaG1-2 or pT1G1), a surveillance programme is strongly advised. In patients considered unfit for surveillance, a modified lymphadenectomy is an optional recommendation.
2. In cases of intermediate risk (pT1G2), vascular or lymphatic invasion and growth pattern can be taken into account for a therapeutic decision making. However, a strict surveillance programme could also be an optional recommendation in patients, assuming there is a reliable regular follow-up.
3. In patients at high risk (pT≥2 or G3), a modified or radical inguinal lymphadenectomy can be strongly recommended.
4. The modified lymphadenectomy can be enlarged to a radical lymphadenectomy if positive nodes are present on frozen section.
5. A sentinel lymph node biopsy with isosulfan blue or/and 99m Tc-colloid sulfur should be considered as an investigational procedure.

SUMMARY GUIDELINES ON TREATMENT OF PALPABLE REGIONAL NODES WITH POSITIVE - HISTOPATHOLOGY

1. Bilateral radical inguinal lymphadenectomy is the standard recommendation. Immediate or delayed pelvic lymphadenectomy could be performed in cases of two or more positive inguinal nodes or extracapsular invasion. A modified lymphadenectomy can initially be considered on contralateral inguinal area with no palpable nodes.
2. Patients with fixed inguinal masses or clinically positive pelvic nodes (CT or MRI) are good candidates for induction chemotherapy followed by radical ilio-inguinal lympahadenectomy. Another strategy is to use pre-operative radiotherapy, but this has complications.
3. When inguinal palpable nodes appear after a surveillance programme, two possible recommendations are made: a) bilateral radical inguinal lymphadenectomy; or b) inguinal lymphadenectomy at the site of positive nodes according to the disease-free interval.
4. Adjuvant chemotherapy is advisable when there are two or more positive nodes or extracapsular nodal involvement. Another option is adjuvant radiotherapy.