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EAU Guidelines on Penile Cancer

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Abstract

Objectives: The European Association of Urology (EAU) consensus group on penile cancer has prepared these guidelines to help urologists assess the scientific evidence for the management of penile cancer and to incorporate recommendations into their clinical practice.

Method: References used in the text have been assessed according to the level of scientific evidence involved and guideline recommendations have also been evaluated according to the Agency for Health Care Policy and Research [Clinical Practice Guidelines Development: Methodological Perspectives. Washington DC: US Department of Health and Human Services, Public Health Service; 1992, pp. 115–127].

Results: The diagnosis, treatment and follow-up of patients suspected of, or diagnosed with, penile cancer is listed as an easy reference text.

Conclusion: A guidelines text is presented which aims at aiding medical specialists in determining the most optimal diagnostic and treatment options for this pathology.

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Keywords: Guidelines; Penile cancer; Classification; Diagnosis; Treatment; Follow-up

1. Background

Penile carcinoma is an uncommon malignant disease, with an incidence of 0.1–0.9 per 100,000 males in Europe and 0.7–0.9 per 100,000 males in the USA. However, in some areas of Asia, Africa and South America, the incidence of penile carcinoma is significantly higher at 19 per 100,000 males [1]; in these countries, penile carcinoma accounts for as much as 10–20% of male cancers.

The localization of the primary tumour appears in the glans in 48% of cases, prepuce in 21%, both glans and prepuce in 9%, coronal sulcus in 6% and the shaft in less than 2% [2]. Palpable inguinal nodes are present at diagnosis in 58% of patients (range 20–96%) [3]. Of these patients, 17–45% actually have nodal metastases, while the remainder have inflammatory disease secondary to infection of the primary tumour ([3,4]: level 2a). The likelihood of bilateral involvement is considerable due to the rich, subcutaneous, lymphatic communications of the penis. About 23–56% of patients with metastases to two or more nodes also have pelvic nodal involvement ([5–7]: level 2b). About 20% of patients with non-palpable nodes have nodal micrometastases. The depth of invasion, corpora cavernosa invasion, tumour grade, vascular and lymphatic involvement and growth pattern and the associations of these factors are risk factors related to the occurrence of nodal metastases ([8,9]: level 2a).

An overall 5-year survival rate of 52% has been reported, ranging from 66% in patients with negative lymph nodes, 27% in patients with positive nodes, and from 0 to 38.4% in patients with pelvic node involvement ([3,6,7,10]: level 2b/2a).

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Table 1
Premalignant lesions and neoplasias of the penis

Premalignant lesions	
Lesions sporadically associated with squamous cell carcinoma of the penis	Cutaneous horn of the penis and Bowenoid papulosis of the penis
Lesions at high risk of developing SCC of the penis	Penile intraepithelial neoplasia (erythroplasia of Queyrat, Bowen's disease) and balanitis xerotica obliterans
Penile neoplasias (SCC)	
Types	Classic, basaloid, verrucous and its varieties (warty, verrucous carcinoma, papillary carcinoma, hybrid verrucous carcinoma), sarcomatoid, adenosquamous
Growth pattern	Superficial spread, nodular or vertical-phase growth, verrucous
Differentiation grades	Broders system (traditional grading) Maiche score system (most suitable grading system)
Mesenchymal tumours (>3%)	Kaposi's sarcoma, angiosarcoma, epitheliod haemangioendothelioma
Metastatic disease (uncommon)	Prostate, rectal, renal tumours reported as primary tumours in metastatic disease

SCC: squamous cell carcinoma.

2. Classification

2.1. Pathology

Squamous cell carcinoma (SCC) is by far the most common malignant disease of the penis (Table 1), accounting for more than 95% of cases. The 1997/2002 TNM classification for penile cancer is shown in Table 2.

3. Risk factors

Phimosis and chronic irritation processes related to poor hygiene are commonly associated with this tumour, whereas neonatal circumcision has a protective effect ([11]: level 2a). There is strong evidence that human papillomavirus types 16 and 18 are associated with penile carcinoma in up to 50% of cases, as well as to penile carcinoma *in situ*, basaloid and warty verrucous varieties in more than 90% ([12]: level 2a).

The prognostic factors most strongly correlated with survival are the presence of positive lymph nodes, the number and site of positive nodes and the extracapsular nodal involvement ([6,10]: level 2a).

Primary tumour parameters (i.e. location, size, tumour grade, corpora cavernosa invasion) are important predictors for the presence of lymph node metastasis in uni- and multivariate analysis [9,13,14], as well the association of some of these parameters ([15]: level 2a). These factors have been used to define high-risk ($\geq$T2 or G3), intermediate-risk (T1G2) and low-risk (Tis, pTaG1–2, pT1G1) groups of patients [13,15]. These prognosis groups have recently been widely accepted in the literature [8,16] and prospectively validated ([15]: level 2a).

Molecular markers are currently under investigation as prognostic factors, but currently have no use in clinical practice [17].

Table 2
1997/2002 TNM classification of malignant tumours

Primary tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situn*
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

4. 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.

4.1. Primary lesion

Patients with a suspicious penile lesion should undergo a detailed physical examination of the penis

Table 3
Diagnostic schedule for penile cancer

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

CT: computerized tomography; MRI: magnetic resonance imaging.
[a] Cabanas technique is no longer advisable. Isosulphan blue or ^{99m}Tc-colloid sulphur is promising new procedure.

(Grade B). Cytology or histological diagnosis is absolutely necessary before making treatment decisions (Grade B), with the aim of determining both the pathological diagnosis and the tumour grade. This information will assist in making therapeutic decisions concerning the primary tumour, as well as in establishing risk groups for regional therapeutic strategy [15].

Diagnostic imaging, ultrasound and MRI (Grade C) can assist in identifying the depth of tumour invasion, particularly with regard to corpora cavernosa infiltration ([18]: level 3).

4.2. Regional nodes

A careful inguinal physical examination is necessary (Grade B), 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 have been observed on the primary tumour, it is advisable to perform pathological surgical inguinal nodal staging (Grade B) (*see later*). Although traditional sentinel node biopsy is unreliable, the recent technique of dynamic sentinel lymph node biopsy with isosulphan blue and/or ^{99m}Tc-colloid sulphur (Grade B) provides a specificity of 100% and a sensitivity of 78–80% [19]. It has also been validated recently in a prospective study ([20]: level 2a/b).

Palpable nodes: As many as 50% of palpable inguinal nodes at diagnosis are reactive and not metastatic. On the contrary, nearly 100% of enlarged nodes appearing during follow-up are metastatic ([3,13]: level 2a). It is therefore suggested that regional nodes should be evaluated a few weeks after treatment of the primary tumour so that the inflammatory reaction can subside. A histological diagnosis involving fine-needle aspiration biopsy, tissue core biopsy, or open biopsy, according to the preference of the pathologist should be performed (Grade B).

Imaging techniques such as computerised tomography (CT) scan and magnetic resonance imaging (MRI) have been and are widely used. However, they are very expensive and are more useful for staging than for early detection. Positron emission tomography (PET) scanning is under investigation.

4.3. Distant metastasis

Distant metastases should only be assessed in patients with proven positive nodes (grade B) [3]. A diagnostic schedule for penile cancer is shown in Table 3.

5. Guidelines on treatment of penile neoplasia

5.1. Primary lesion

Category Ta–1G1–2: In these cases, a penis-preserving strategy is strongly recommended, particularly for patients who can guarantee a regular follow-up (Grade B), including the following strongly recommended therapies: laser therapy (CO_2 or Neodynium:Yttrium-Aluminum-Garnet [Nd-YAG]), cryotherapy, photodynamic therapy, topical imiquimod 5% or 5-fluorouracil (5-FU) cream, local excision and Mohs' surgery plus reconstructive surgery, radiotherapy or brachytherapy, and glansectomy ([21–27]: level 2a).

The therapeutic approach should be decided according to the surgeon's and patient's preferences and the available technology. There is no difference in the local recurrence rate (15–25%) comparing different methods. With traditional conservative surgery, the recurrence rate is more variable from 11 to 50% [23]. A pathological assessment of surgical margins is

essential in applying these procedures and in achieving a decrease in local recurrence of 9–24% ([21]: level 2b).

In patients who do not comply with regular follow-up, partial amputation is an optional recommendation (Grade B).

Category T1G3, ≥T2: Partial or total amputation or emasculation (Grade B) according to tumour extent can be considered to be standard therapies ([16,23,26]: level 2a). A conservative strategy is an alternative in very carefully selected patients whose tumours encompass less than half of the glans (Grade B) and for who close follow-up can be carried out ([25]: level 2b). Chemotherapy induction courses within the context of a clinical trial, followed by conservative procedures in cases of complete or partial response (Grade C), can be considered an investigational recommendation ([24,28]: level 3).

Local disease recurrence: For local recurrence after conservative therapy, partial or total penectomy is recommended (Grade B). A second conservative procedure is strongly advised if no corpora cavernosa invasion is present (Grade B) ([27]: level 2b).

5.2. Regional nodes

Although inguinal lymphadenectomy is a proven treatment, its high morbidity precludes its prophylactic use.

Non-palpable nodes: According to prognostic factors from uni- and multivariate analysis, three patient risk groups have been identified ([13,15,16]: level 2a).

In patients at low risk of developing nodal micrometastases (pTis, pTaG1–2 or pT1G1), a surveillance programme is strongly advised (Grade B), as the probability of occult micrometastases occurring in inguinal lymph nodes is less than 16.5% ([15,29]: level 2a). If patients are considered unsuitable for surveillance, a 'modified' inguinal lymphadenectomy is suggested as an optional recommendation (Grade B).

In cases of intermediate risk (T1G2), vascular or lymphatic invasion and growth pattern should be taken into account when making therapeutic decisions ([8,9,14]: level 2a). The high reliability of dynamic sentinel node biopsy, as demonstrated in recent reports ([20]: level 2a), means that this method can be used instead of predictive factors to identify patients suitable for a modified lymphadenectomy in this group (Grade B) (Table 4).

In patients at high risk of nodal involvement (≥T2 or G3), modified or radical inguinal lymphadenectomy can be strongly recommended (Grade B). In these patients, the incidence of occult metastases ranges between 68% and 73% ([13,15,29]: level 2a).

A modified lymphadenectomy can be extended to a radical lymphadenectomy if positive nodes are present on frozen sections.

Palpable nodes with positive histopathology: Bilateral radical inguinal lymphadenectomy is strongly recommended for positive palpable nodes (Grade B). Immediate or delayed pelvic lymphadenectomy can be performed in cases where two or more positive inguinal lymph nodes or extracapsular invasion are found on frozen section biopsy or standard pathology examination (Grade B). In these cases, the probability of pelvic lymph nodes is 23% when two or three inguinal nodes are involved and 56% when more than three nodes are involved ([5]: level 2b). In these cases, metastases are often microscopic and offer the possibility of cure in 14–54% ([3,7]: level 2b). On the contralateral inguinal area with no palpable nodes, modified lymphadenectomy can initially be considered and may be extended if positive nodes are found upon frozen section biopsy.

For patients with fixed inguinal masses or clinically positive pelvic nodes (CT scan or MRI), induction chemotherapy can give an objective response in 21–60% of cases; if followed by subsequent radical ilio-inguinal lymphadenectomy, it is strongly recommended (Grade B) ([4,5,8,30]: level 2b/3). Another strategy is to use pre-operative radiotherapy [31,32] but the increased morbidity of lymphadenectomy after radiotherapy should be considered (Grade C) ([26]: level 3).

When inguinal palpable nodes appear after a surveillance programme, two strong recommendations for treatment are made (Grade B):

- Bilateral radical inguinal lymphadenectomy, following similar criteria to that discussed above.
- Inguinal lymphadenectomy, performed at the site of positive nodes in the case of a long disease-free interval. In these cases, the contralateral inguinal recurrence is around 10%, but a follow-up programme is advised. However, when there is more than one pathological lymph node in unilateral lymphadenectomy, the probability of occult contralateral involvement is approximately 30% and warrants an early bilateral inguinal lymphadenectomy ([6]: level 3).

  Adjuvant therapy is advised (Grade C) when there are two or more positive nodes or extracapsular nodal involvement on pathological examination, as the prognosis of these patients is poorer than in patients with a single, positive lymph node ([6]: level 2b). Fewer data are available on adjuvant radiotherapy ([32]: level 3).

Table 4
Therapeutic schedule for penile cancer

Lesion level	Therapy	Recommendations		
		Strong	Optional	Investigational
Primary tumour	Conservative therapy	Primary/recurrent Tis, Ta–1G1–2	T1G3, T2 limited to <50% of glans (fit patients for surveillance)	After chemotherapy, according to tumour response
	Total/partial amputation Radiotherapy	Primary/recurrent T1G3, ≥T2 T1–2 < 4 cm	Primary or recurrent Ta–1G1–2 (conservative therapy not feasible), amputation refusal	In combination with chemotherapy
Regional (non-palpable nodes)	Surveillance	Tis, TaG1–2, T1G1, T1G2 Superficial growth, vascular (−ve) or negative dynamic sentinel node biopsy	T2G2–3 (Preference and fit patients for close follow-up)	
	Modified LND[a]	T1G2 nodular growth or vascular (+ve) or positive dynamic sentinel node biopsy, T1G3 or any T2	T1G2 vascular (−ve) flat growth or negative dynamic sentinel node biopsy (unfit patients for follow-up)	
Regional (palpable nodes)	Radical LND[b]	Positive nodes at presentation Positive nodes after surveillance	Plus adjuvant chemotherapy[c] or radiotherapy[d] (>1 positive node) Unilateral LND on nodal site (disease-free interval >6 months and <3 positive nodes)	
	Chemotherapy +ve/−ve LND[c]	Fixed inguinal masses, pelvic nodes (fit patients for chemotherapy)		
	Radiotherapy[d] +ve/−ve 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.

5.3. 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 first and then radical or palliative surgery or radiotherapy when indicated, according to the tumour response.

5.4. Distant metastases

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

5.5. Quality of life

Regarding partial penectomy, a negative impact on quality of life was observed in European patients on general health, anxiety, social problems and sexual function domains ([23]: level 2a). Age, performance status, socio-economic context, psychological status, sexual function, patient motivation and the morbidity of different procedures should be considered as part of the decision-making process, as penile carcinoma is a malignant disease with a high probability of cure but a high degree of therapeutic morbidity.

5.6. Technical aspects

- With the primary lesion, the simplicity and morbidity of the procedure and the 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 traditionally required removal of 2-cm tumour-free margins. Although this is probably more than is necessary, it is essential to achieve free tumour margin with pathological confirmation. A surgical margin of 10 mm would be safe, but should be 1.5 cm for G3 ([33]: level 2b).

- 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. With these modifications, complications and morbidity rates are lower than radical ilio-inguinal lymphadenectomy, providing a safe procedure ([34]: level 2b).
- Morbidity from lymphadenectomy for penile cancer remains high despite improved surgical skills: thicker and less extensive skin flaps may reduce skin necrosis, femoral vessels can be protected by coverage with the sartorius muscle, better lymphatics control and preservation of the saphenous vein may decrease leg oedema, per- and post-operative anticoagulation can prevent deep venous thrombosis and pulmonary embolism [35].
- Pelvic lymphadenectomy includes the external iliac lymphatic chain and ilio-obturator chain (proximal boundary: iliac bifurcation; lateral: ilio-inguinal nerve; medial: obturator nerve).

5.7. Chemotherapy

The chemotherapy regimen should be discussed with the medical oncologist and it is suggested that this strategy be adopted within the context of clinical trials. However, the following can be used as guidelines.

Adjuvant chemotherapy: Two courses of cisplatin and 5-FU may be sufficient. Alternatively, vincristine, methotrexate and bleomycin may be administered once a week for 12 weeks on an outpatient basis [4,30]. Analysis has identified the following risk factors: none of the category pN1 patients relapsed, independently of adjuvant or no adjuvant chemotherapy; relapses occurred after adjuvant chemotherapy (50%) only in patients with bilateral and/or pelvic metastases ([4,30]: level 2b).

Neoadjuvant chemotherapy for fixed inguinal nodes: induction chemotherapy comprised of three to four courses of cisplatin and 5-FU in appropriate dosages and sequence. Overall, combining all series using this approach, the response rate was 68.5%, the radical surgery rate was 42.8% and the survival rate was 23% ([5]: level 2b).

Chemotherapy for advanced disease: This has not been widely used in penile cancer. Different cisplatin-based chemotherapy schemes associated with 5-FU, bleomycin or methotrexate [5] have usually achieved modest results, with 32% complete and partial response rate and 12% treatment-related deaths in the most recent study [36]. Intra-arterial chemotherapy in locally advanced or recurrent SCC of the penis is promising [37], both as palliative treatment or neoadjuvant therapy. A therapeutic schedule for penile cancer is shown in Table 4.

5.8. Radiotherapy

Primary tumour: External beam radiotherapy or brachytherapy has produced a complete response rate of 56% and 70%, respectively. Although local failure rates were 40% and 16%, respectively, salvage surgical resection may restore local control. Common complications include meatal stenosis in 15–30%, urethral structures in 20–35%, and telangiectasias in greater than 90%. Post-radiation changes include necrosis that is clinically difficult to differentiate from persistent tumour [5].

Prophylactic radiotherapy in clinically negative lymph nodes is not recommended for the following reasons:

- Radiotherapy fails to prevent the development of metastatic lymph nodes [31,32].
- Complications of radiotherapy [6,26].
- Follow-up is more difficult due to fibrotic changes.

Pre-operative radiotherapy in patients with fixed nodes can render them operable, but it is not known whether the fixation is an inflammatory reaction or malignant growth [6,26,32].

Adjuvant radiotherapy may be used for metastastic nodes to reduce local recurrence [32].

Table 4 provides a therapeutic schedule for penile cancer.

6. Guidelines for follow-up in penile cancer

Penile carcinoma is one of the few solid tumours for which lymphadenectomy can provide a high cure rate even if lymph nodes are involved. Urologists are faced with the dilemma of reaching an appropriate balance between decreasing morbidity using conservative procedures and disease control. Follow-up is therefore crucial if similar survival rates are to be achieved with early or delayed lymphadenectomy. Most relapses occur during the first 2 years, but late recurrences still appear [38]. As penile carcinoma is sometimes associated with poor socio-economic conditions, close surveillance is not always possible.

6.1. Why follow-up?

With respect to the primary lesion, the local disease recurrence rate with partial or total penectomy ranges from 0–7% [23]; with conservative therapies, this might

increase to 50% [23]. Nevertheless, local disease recurrence does not have a negative impact on cause-specific survival, provided early diagnosis is carried out [24].

Controversy remains as to whether early or delayed lymphadenectomy should be carried out in patients with initially non-palpable inguinal lymph nodes. Some authors achieve similar survival rates with both approaches [1]. However, a surveillance programme implies a close follow-up because late diagnosis seems to be a negative prognostic factor [29].

6.2. How to follow-up?

As penile and inguinal lymph nodes are externally situated, patient follow-up with penile carcinoma is based essentially on inspection and physical evaluation. CT scan and chest radiographs are additional tests to identify pelvic lymph nodes or distant metastases, particularly in categories equal or more than N2 as the tumour spreads mainly in these areas. Other diagnostic tests should be used in symptomatic patients.

6.3. 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 regional lymph nodes. Table 5 provides a follow-up schedule for penile cancer.

6.4. Primary tumour

If the primary lesion was treated with conservative therapy, an initial follow-up schedule is recommended because most local recurrences occur during the first 2 years (Grade C). Long-term follow-up is also recommended because late local recurrences have been observed [38]. Patient self-evaluation is advisable; patients should be informed about the possible warning signals.

If patients have been treated with partial or total penectomy, the follow-up schedule is different (Grade C) because local disease recurrence, although uncommon, usually occurs very early and because an early diagnosis is necessary due to the aggressive behaviour of the tumour [39].

6.5. Regional areas

The follow-up schedule is based on the fact that most inguinal lymph node recurrences are detected during the first 2 years (Grade C). Moreover, when recurrences develop, their growth is very quick and the prognosis is related to the number, size and bilateralism of the lymph nodes [10]. Very close follow-up is therefore advisable.

If inguinal lymphadenectomy has been performed with no tumour detected on pathological examination, a local or distant relapse is rare in cases where a radical procedure and extensive pathological examination have been performed. The follow-up is focused essentially on the quality of life for these patients as inguinal lymphadenectomy has a high morbidity rate. If positive lymph nodes were observed on pathological examination, specific follow-up cannot be recommended (Grade C), as many variables need to be considered, including:

- Number of positive lymph nodes (uni- or bilateral).
- Whether pelvic lymphadenectomy was performed, with or without positive lymph nodes.
- Whether adjuvant therapy was carried out and the scheme used.

In relation to these variables, each treatment centre should define the physical examination, CT scan, chest radiograph and the appropriate intervals between them.

Bone scan and other tests are only recommended in symptomatic patients (Grade B). Quality of life assessment should essentially encompass sexual activity and lymphadenectomy morbidity (lymphoedma).

Table 5
Follow-up schedule for penile cancer

Lesion level	Therapy	Interval			Examinations	
		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 +ve)	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: computerized 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.

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