Guidelines on
Penile Cancer

E. Solsona, F. Algaba, S. Horenblas, G. Pizzocaro, T. Windahl

European
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1. INTRODUCTION

The European Association of Urology (EAU) consensus group on penile cancer has prepared these guidelines[1] to help urologists assess the scientific evidence for the management of penile cancer and to incorporate recommendations into their clinical practice. References used in the text have been assessed according to the level of scientific evidence involved, as indicated by Table 1. Guideline recommendations have also been evaluated (Table 2), according to the Agency for Health Care Policy and Research (1).

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 quasi-experimental study
3	Evidence obtained from well-designed non-experimental 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

Table 2: Grades of guideline recommendations (1)

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

1.1 REFERENCE

1. 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.
http://www.ahcpr.gov/clinic/epcindex.htm#methodology

2. BACKGROUND

Penile carcinoma is an uncommon malignant disease, with an incidence of 0.1-7.9 per 100,000 males. In Europe, the incidence is 0.1-0.9 per 100,000, and in the USA, 0.7-0.9 per 100,000. In some areas of Asia, Africa and South America, the incidence is significantly higher at 19 per 100.000 (1); in these countries, penile carcinoma accounts for as many as 10-20% of male cancers.

Penile carcinoma essentially metastasizes via the lymphatic system and develops mainly through an embolization mechanism instead of lymphatic permeation. Distant metastases are very rare and are a result of vascular dissemination (2). Spreading essentially develops in stepwise fashion; inguinal lymphatic spread occurs first, followed by pelvic metastases, and lastly by 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 primary tumour is localized to 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 (3). Palpable inguinal nodes are present at diagnosis in 58% of patients (range 20-96%) (4). Of these patients, 17-45% have nodal metastases, while the remaining patients have inflammatory disease secondary to an infection of the primary tumour (4-6) (level of evidende: 2a).

The likelihood of bilateral involvement is considerable because of the large number of penile lymphatics in the subcutaneous tissue. Pelvic nodal involvement is found in 22-56% of patients with metastases to two or more nodes (7-9) (level of evidence: 2b). About 20% of patients with non-palpable nodes harbour nodal micrometastases. The occurrence of nodal metastases is affected by the depth of invasion, tumour grade, vascular and lymphatic involvement, corpora cavernosa involvement and growth pattern and the associations of these factors (10-12) (level of evidence: 2a).

An overall 5-year survival rate of 52% has been reported. This ranges from 66% in patients with negative lymph nodes to 27% in patients with positive nodes (4,6,8,13-15) (level of evidence: 2a), and 0-38.4% in patients with pelvic node involvement (4,8,9,16) (level of evidence: 2b). 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 the management of penile cancer. Treatment of the primary tumour tends to be more organ-preserving, in order to maintain sexual function and a better quality of life (1,15,17-19) (level of evidence: 2b). There is also debate about the need and extent of lymphadenectomy in clinically node-negative patients (1,20). Social and cultural habits also seem to be important factors in penile cancer, as exemplified by the fact that 44-90% of patients suffer from phimosis at presentation (2) and the documented association between human papillomavirus (HPV) and penile carcinoma (21-23) (level of evidence: 2a).

All these factors, together with the low incidence rate in countries with good socio-economic conditions and the absence of large or randomized trials, have an important influence on the management of penile cancer.

2.1 Classification

2.1.1 Pathology

Squamous cell carcinoma (SCC) 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. The extent to which SCC is preceded by pre-malignant lesions (3,24) (Table 3) is unknown. Although SCC is the most common penile neoplasia, it manifests in several different types and with varying growth patterns (24-26) (Table 4).

Mesenchymal tumours are very uncommon (3), with an incidence rate of less than 3% (e.g. Kaposi's sarcoma, angiosarcoma, epithelioid haemangioendothelioma).

The penis is a very rare metastatic site, but bladder, prostate, renal and rectal tumours have been reported as primary tumours in cases of metastatic disease (3).

Table 3: Premalignant lesions

Lesions sporadically associated with SCC of the penis (3,24) (level of evidence: 2b)
• Cutaneous horn of the penis
• Bowenoid papulosis of the penis
Lesions at high risk of developing SCC of the penis (up to one-third transform to invasive SCC) (24) (level of evidence: 2a)
• Penile intraepithelial neoplasia (consider carcinoma *in situ*) (erythroplasia of Queyrat, Bowen's disease)
• Balanitis xerotica obliterans

Table 4: Penile neoplasias (SCC)

Types of SCC
• Classic
• Basaloid

• Verrucous and its varieties (24):
  • Warty (condylomatous) carcinoma
  • Verrucous carcinoma
  • Papillary carcinoma
  • Hybrid verrucous carcinoma
  • Mixed carcinomas (warty-basaloid carcinoma, adeno-basaloid carcinoma)

• Sarcomatoid
• Adenosquamous
Growth patterns of SCC
• Superficial spread
• Nodular or vertical-phase growth
• Verrucous
Differentiation grading systems for SCC
• Broders system (25): traditionally used as a grading system
• Maiche system score (26): currently seems to be the most suitable grading system

2.1.2 TNM staging

The 1997 and 2002 Tumour Node Metastasis (TNM) classification for penile cancer is shown in Table 5 (27).

Table 5: The 1997/2002 TNM (Tumour, Node, Metastasis) classification of penile cancer (27)

T - 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
N - 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
M - Distant metastasis	
MX	Distant metastases cannot be assessed
M0	No evidence of distant metastases
M1	Distant metastases

2.2 REFERENCES

1. Mobilio, G, Ficarra, V. Genital treatment of penile carcinoma. Curr Opin Urol 2001;11:299-304. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11371784&dopt=Abstract
2. Burgers JK, Badalament RA, Drago JR. Penile cancer. Clinical presentation, diagnosis and staging. Urol Clin North Am 1992;19:247-256. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1574815&dopt=Abstract
3. Sufrin G, Huben R. Benign and malignant lesions of the penis. In: *Adult and Pediatric Urology* 2nd edn. Gillenwater JY (ed). Chicago: Year Book Medical Publisher, 1991, pp. 1643.
4. Ornellas AA, Seixas ALC, Marota A, Wisnescky A, Campos F, de Moraes JR. Surgical treatment of invasive squamous cell carcinoma of the penis: retrospective analysis of 350 cases. J Urol 1994;151:1244-1249. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7512656&dopt=Abstract
5. Horenblas S, Van Tinteren H, Delamarre JFM, Lustig V, Van Waardenburg FW. Squamous cell carcinoma of the penis. III. Treatment of regional lymph nodes. J Urol 1993;149:492-497. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8437253&dopt=Abstract
6. Pizzocaro G, Piva L, Nicolai N. Treatment of lymphatic metastasis of squamous cell carcinoma of the penis at the National Tumor Institute of Mila. Arch Ital Urol Androl 1996;68:169-172. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8767505&dopt=Abstract
7. Culkin DJ, Beer TM. Advanced penile carcinoma. J Urol 2003;170:359-365. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12853775&dopt=Abstract
8. Horenblas S. Lymphadenectomy for squamous cell carcinoma of the penile. Part 2: the role and technique of lymph node dissection. BJU Int 2001;88:473-483. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11589660&dopt=Abstract
9. Lopes A, Bezerra AL, Serrano SV, Hidalgo GS. Iliac nodal metastases from carcinoma of the penis treated surgically. BJU Int 2000;86:690-693. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11069378&dopt=Abstract

10. Emerson RE, Ulbright TM, Eble JN, Geary WA, Eckert GJ, Cheng L. Predicting cancer progression in patients with penile squamous cell carcinoma: the importance of depth of invasion and vascular invasion. Med Pathol 2001;14:963-968. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11598165&dopt=Abstract
11. Ficarra V, Martignoni G, Maffei N, Cerruto MA, Novara G, Cavalleri S, Artibani W. Predictive pathological factors of lymph nodes involvement in the squamous cell carcinoma of the penis. Int Urol Nephrol 2002;34:245-250. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12775105&dopt=Abstract
12. Slaton JW, Morgenstern N, Levy DA, Santos MW Jr, Tamboli R, Ro JY, Ayala AG, Pettaway CA. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal lymph node metastasis in penile squamous cancer J Urol 2001;165:1138-1142. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11257655&dopt=Abstract
13. Derakshani P, Neubauer S, Braun M, Bargmann H, Heidenreich A, Engelmann U. Results and 10-year follow-up in patients with squamous cell carcinoma of the penis. Urol Int 1999;62:238-244. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10567892&dopt=Abstract
14. Demkow T. The treatment of penile carcinoma: experience in 64 cases. Int Urol Nephrol 1999;31:525-531. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10668948&dopt=Abstract
15. Hakenberg OW, Wirth MP. Issues in the treatment of penile carcinoma. A short review. Urol Int 1999;62:229-233. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10567890&dopt=Abstract
16. Ravi R. Correlation between the extent of nodal involvement and survival following groin dissection for carcinoma of the penis. Br J Urol 1993;72:817-819. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8281416&dopt=Abstract
17. Ficara V, Maffei N, Piacentine I, Al Rabi N, Cerruto MA, Artibani W. Local treatment of penile squamous cell carcinoma. Urol Int 2002;69:169-173. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12372882&dopt=Abstract
18. Schoeneich G, Perabo FGE, Muller SC. Squamous cell carcinoma of the penis. Andrologia 1999;31(Suppl 1):17-20. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10643514&dopt=Abstract
19. Stancik I, Holtl W. Penile cancer: review of the recent literature. Curr Opin Urol 2003;13:467-472. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14560140&dopt=Abstract
20. Wilbert DM. (Lymph node metastases in penis carcinoma. Therapeutic options and outcome.) Urologe A 1999;38:332-336. [German] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10444790&dopt=Abstract
21. Bezerra AL, Lopes A, Landman G, Alencar GN, Torloni H, Villa LL. Clinicopathologic features and human papillomavirus DNA prevalence of warty and squamous cell carcinoma of the penis. Am J Surg Pathol 2001;25:673-678. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11342782&dopt=Abstract
22. Dillner J, von Krogh G, Horenblas, S, Meijer CJ. Etiology of squamous cell carcinoma of the penis. Scand J Urol Nephrol Suppl, 2000;205:189-193. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11144896&dopt=Abstract

23. Picconi MA, Eijan AM, Distefano AL, Pueyo S, Alonio LV, Gorostidi S, Teyssie AR, Casaba A. Human papillomavirus (HPV) DNA in penile carcinomas in Argentina: analysis of primary tumors and lymph nodes. J Med Virol 2000;61:65-69. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10745234&dopt=Abstract
24. Cubilla AL, Reuter V, Velazquez E, Piris A, Saito S, Young RH. Histologic classification of penile carcinoma and its relation to outcome in 61 patients with primary resection. Int J Surg Pathol 2001;9:111-120. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11484498&dopt=Abstract
25. Broders AC. Squamous cell epithelioma of the skin. Ann Surg 1921;73:141.
26. Maiche AG, Pyrhönen S, Karkinen M. Histological grading of squamous cell carcinoma of the penis: a new score system. Br J Urol 1991;67:522-526. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1710163&dopt=Abstract
27. Sobin LH, Wittekind Ch. TNM Classification of Malignant Tumors. 6th edn. New York: Wiley-Liss, 2002. www.wiley.com/go/tnm

3. RISK FACTORS FOR PENILE CARCINOMA

Phimosis and chronic irritation processes related to poor hygiene are commonly associated with this tumour, whereas neonatal circumcision gives protection against the disease (1) (level of evidence: 2a). There is strong evidence that HPV types 16 and 18 are associated with penile carcinoma in as many as 50% of cases, as well as with penile carcinoma *in situ*, and basaloid and warty verrucous varieties in more than 90% of cases (1-3) (level of evidence: 2a).

The best prognostic factors related to survival are the presence of positive lymph nodes, the number and site of positive nodes and the extracapsular nodal involvement (4-9) (level of evidence: 2a). These are therefore important factors to consider when applying complementary therapies following lymphadenectomy pathological examination.

Predictive factors for the presence of lymph node metastasis have been assessed thoroughly. Important predictive factors include parameters from the primary tumour, i.e. location, size, tumour grade, corpora cavernosa invasion (10,11) and the association of some of these factors (12). These factors have been corroborated by multivariate analysis (7,8,13-15) (level of evidence: 2a), and have been used to define high-, intermediate- and low-risk groups for lymph node metastasis (9,11,12). These risk groups have recently been widely accepted in the literature (13,16,17) and prospectively validated (18) (level of evidence: 2a). Other important predictive factors with particular relevance in the intermediate-risk group include vascular, lymphatic invasion, depth of invasion and growth pattern of the primary tumour (19,20). All these factors have been taken into account when outlining the therapy recommendations given in these guidelines (see 5.2.1 Non-palpable nodes).

Molecular markers are under investigation as prognostic factors, but they currently have no use in clinical practice (21-23). More promising results have been reported with p-53 overexpression (22,24) and SCC antigen in predicting nodal involvement (25); nonetheless, these results need to be prospectively validated before they can be incorporated into clinical practice.

3.1 REFERENCES

1. Dillner J, Meijer CJ, von Krogh G, Horenblas S. Epidemiology of human papillomavirus infection. Scand J Urol Nephrol Suppl 2000;205:194-200. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11144898&dopt=Abstract
2. Bezerra AL, Lopes A, Landman G, Alencar GN, Torloni H, Villa LL. Clinicopathologic features and human papillomavirus DNA prevalence of warty and squamous cell carcinoma of the penis. Am J Surg Pathol 2001;25:673-678. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11342782&dopt=Abstract

3. Picconi MA, Eijan AM, Distefano AL, Pueyo S, Alonio LV, Gorostidi S, Teyssie AR, Casabe A. Human papillomavirus (HPV) DNA in penile carcinomas in Argentina: analysis of primary tumors and lymph nodes. J Med Virol 2000;61:65-69. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10745234&dopt=Abstract
4. Ravi R. Correlation between the extent of nodal involvement and survival following groin dissection for carcinoma of the penis. Br J Urol 1993;72:817-819. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8281416&dopt=Abstract
5. Ricos Torrent JV, Ramon-Borja JC, Iborra Juan I, Monros Lliso JL, Dumont Martinez R, Solsona Narbon E. (Locoregional treatment of carcinoma of the penis.) Arch Esp Urol 1991;44:667-682. [Spanish] http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1722961&dopt=Abstract
6. Srinivas V, Morse M, Herr E, Sogani P, Whitmore W Jr. Penile cancer: relation of extent of nodal metastasis to survival. J Urol 1987;137:880-882. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3573181&dopt=Abstract
7. Sarin R, Norman AR, Steel GG, Horwich A. Treatment results and prognostic factors in 101 men treated for squamous carcinoma of the penis. Int J Radiat Oncol Biol Phys 1997;38:713-722. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9240637&dopt=Abstract
8. Soria JC, Fizazi K, Piron D, Kramar A, Gerbaulet A, Haie-Meder C, Perrin JL, Court B, Wibault P, Theodore C. Squamous cell carcinoma of the penis: multivariate analysis prognostic factors and natural history in monocentric study with a conservative policy. Ann Oncol 1997;8:1089-1098. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9426328&dopt=Abstract
9. Horenblas S. Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: the role and technique of lymph node dissection. BJU Int 2001;88:473-483. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11589660&dopt=Abstract
10. Horenblas S, Van Tinteren HV. Squamous cell carcinoma of the penis. IV. Prognostic factors of survival: analysis of tumor, nodes and metastasis classification system. J Urol 1994;151:1239-1243. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8158767&dopt=Abstract
11. Pizzocaro G, Piva L, Bandieramonte G, Tana S. Up-to-date management of carcinoma of the penis. Eur Urol 1997;32:5-15. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9266225&dopt=Abstract
12. Solsona E, Iborra I, Ricós JV, Monros JL, Dumont R, Casanova J, Calabuig C. Corpus cavernosum invasion and tumor grade in the prediction of lymph node condition in penile carcinoma. Eur Urol 1992;22:115-118. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1478225&dopt=Abstract
13. Ficarra V, Martignoni G, Maffei N, Cerruto MA, Novara G, Cavalleri S, Artibani W. Predictive pathological factors of lymph nodes involvement in the squamous cell carcinoma of the penis. Int Urol Nephrol 2002;34:245-250. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12775105&dopt=Abstract
14. Lopes A, Hidalgo GS, Kowallski LP, Torloni H, Rossi BM, Fonseca FP. Prognostic factors in carcinoma of the penis: multivariate analysis of 145 patients treated with amputation and lymphadenectomy. J Urol 1996;156:1637-1642. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8863559&dopt=Abstract
15. Slaton JW, Morgenstern N, Levy DA, Santos MW Jr, Tamboli P, Ro JY, Ayala AG, Pettaway CA. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal lymph node metastasis in penile squamous cancer. J Urol 2001;165:1138-1142. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11257655&dopt=Abstract

16. Akduman B, Fleshner NE, Ehrlich L, Klotz L. Early experience in intermediate-risk penile cancer with sentinel node identification using the gamma probe. Urology 2001;58:65-68. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11445481&dopt=Abstract
17. Stancik I, Holtl W. Penile Cancer: review of the current literature. Curr Opin Urol 2003 Nov;13(6): 467-472. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14560140&query_hl=37&itool=pubmed_docsum
18. Solsona E, Iborra I, Rubio J, Casanova JL, Ricos JV, Calabuig C. Prospective validation of the association of local tumor stage grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. J Urol 2001;165:1506-1509. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11342906&dopt=Abstract
19. Cubilla AL, Reuter V, Velazquez E, Piris A, Saito S, Young RH. Histologic classification of penile carcinoma and its relation to outcome in 61 patients with primary resection. Int J Surg Pathol 2001;9:111-120. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11484498&dopt=Abstract
20. Villavicencio H, Rubio Briones J, Regalado R, Chechile G, Algaba F, Palou J. Grade, local stage and growth pattern as prognostic factors in carcinoma of the penis. Eur Urol 1997;32:442-447. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9412803&dopt=Abstract
21. Alves G, Heller A, Fiedler W, Campos MM, Claussen U, Ornellas AA, Liehr T. Genetic imbalances in 26 cases of penile squamous cell carcinoma. Genes Chromosomes Cancer 2001;31:48-53. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11284035&dopt=Abstract
22. Lam KY, Chan KW. Molecular pathology and clinicopathologic features of penile tumors: with special reference to analyses of p21 and p53 expression and unusual histologic features. Arch Pathol Lab Med 1999;123:895-904. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10506441&dopt=Abstract
23. Ornellas AA, Mendes Campos M, Ornellas MH, Wisnescky A, Koifman N, Cabral Harab R. (Penile cancer: flow cytometry study of ploidies in 90 patients.) Prog Urol 2000;10:72-77. [French] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10785922&dopt=Abstract
24. Martins AC, Faria SM, Cologna AJ, Suaid HJ, Tucci S Jr. Immunoexpression of p53 protein and proliferating cell nuclear antigen in penile carcinoma. J Urol 2002;167:89-92. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11743282&dopt=Abstract
25. Laniado ME, Lowdell C, Mitchell H, Christmas TJ. Squamous cell carcinoma antigen: a role in the early identification of nodal metastases in men with squamous cell carcinoma of the penis. BJU Int 2003;92:248-250. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12887477&dopt=Abstract

4. DIAGNOSIS

In order to establish a rational diagnostic approach to penile cancer, it is important to take into account the primary lesion, regional lymph nodes and distant metastases, both initially and during follow-up.

4.1 Primary lesion

Patients with a suspicious penile lesion should undergo physical examination. This is often sufficient to determine the diagnosis and staging, as well as aiding therapeutic decision-making. It is important to record:

- diameter of the penile lesion or suspicious areas
- location(s) on the penis
- number of lesions

- morphology of the lesion, whether papillary, nodular, ulcerous or flat
- relationship with other structures (e.g. submucosa, corpora spongiosa and/or cavernosa, urethra)
- colour and boundaries of lesion.

Cytology or histological diagnosis is absolutely necessary before making treatment decisions. The aim is not only to confirm the pathological diagnosis, but also to determine the tumour grade. The information will assist in making therapeutic decisions concerning the primary tumour, as well as in establishing risk groups for regional therapeutic strategy (1). The preference of the pathologist should be taken into account when choosing 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 for a small lesion located in the prepuce or in another feasible area.

Diagnostic imaging, ultrasound or magnetic resonance imaging (MRI) can assist in identifying the depth of tumour invasion, particularly with regard to corpora cavernosa infiltration (2,3) (level of evidence: 3). However, penile ultrasound imaging is sometimes difficult to interpret and is an unreliable method for detecting microscopic infiltration (4).

4.2 Regional nodes

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

4.2.1 Non-palpable nodes

There is no indication for imaging or histological examination if the nodes are non-palpable. If poor prognostic factors were observed with the primary tumour, it is advisable to perform pathological surgical inguinal nodal staging *(see later)*. Nevertheless, sentinel node biopsy, as described by Cabanas (5), is not recommended because false-negative rates have been reported as high as 25% (range 9-50%) (6). However, there have been recent reports of a dynamic sentinel lymph-node biopsy, using isosulphan blue and/or ^{99m}Tc-colloid sulphur, which is a promising, new procedure (7,8). The preliminary results have been corroborated with a specificity of 100% and a sensitivity of 78-80% (9-12) and have recently been validated in a prospective study (13) (level of evidence: 2a). The sensitivity and specificity of this method need to be confirmed in randomized studies.

4.2.2 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 masses
- relationship to other structures (e.g. skin, Cooper ligament) with respect to infiltration, perforation, etc.
- presence of oedema on leg and/or scrotum.

As many as 50% of palpable inguinal nodes at diagnosis are reactive nodes rather than metastatic. In contrast, nearly 100% of enlarged nodes that appear during follow-up are metastatic (14-16) (level of evidence: 2a). Thus, regional nodes should be evaluated a few weeks after treatment of the primary tumour, in order to allow the inflammatory reaction to subside.

The histological diagnosis involves fine-needle aspiration biopsy, tissue core biopsy, or open biopsy according to the preference of the pathologist (17,18) (level of evidence: 2b). In case of a negative biopsy and clinically suspicious nodes, a repeat biopsy or excisional biopsy should be performed. Imaging techniques (computed tomography (CT) scan, MRI) have been used. They continue to be widely used, but are very expensive and more useful for staging than for early detection. Positron emission tomography (PET) scan is under investigation (19).

4.3 Distant metastases

An assessment of distant metastases should only be performed in patients with proven positive nodes (20,21) (level of evidence: 2b). Pelvic/abdominal CT scanning is used in the identification of pelvic and/or retroperitoneal nodes in patients with inguinal metastases. Although this is not a reliable diagnostic method (22), the detection of pelvic masses has a considerable impact on therapy and prognosis (23,24). A chest radiograph should be performed on patients with positive lymph nodes. Routine blood determinations should be carried out only in patients with bulky inguinal masses and pelvis nodes, and in those with metastasis (25,26). A bone scan is recommended only in symptomatic cases (20). A diagnostic schedule is summarized in Table 6.

Table 6: Diagnosis schedule for penile cancer

Lesion level	Procedures		
	Mandatory	**Advisable**	**Optional**
Primary tumour	Physical examination Cytological or histological diagnosis	Ultrasound (if corpora cavernosa invasion suspected)	MRI (if ultrasound inconclusive)
Regional disease • Non-palpable nodes • Palpable nodes	Physical examination Cytological or histological diagnosis	Dynamic sentinel node biopsy[1]	
Distant metastases		Pelvic CT (if inguinal nodes +ve) Abdominal CT (if pelvic nodes +ve) Chest radiography (if nodes +ve)	Bone scan (in symptomatic patients)

CT = computed tomography; MRI = magnetic resonance imaging.
[1] Cabanas technique (5) is no longer advisable. Isosulphan blue or ^{99m}Tc-colloid sulphur is a promising new procedure (7-13).

4.4 Guidelines for the diagnosis of penile cancer

Primary tumour	
1.	Physical examination is mandatory, recording morphological and characteristics of physical lesion (grade B recommendation)
2.	Cytological or histological diagnosis is also mandatory (grade B recommendation)
3.	Imaging: penile ultrasound is advisable to demonstrate corpora cavernosa invasion. In cases of inconclusive results, ultrasound or MRI is an optional method (grade C recommendation)
Regional lymph nodes	
1.	Physical examination is mandatory (grade B recommendation)
2.	If nodes are non-palpable, there is no indication for imaging or histological examination. A new technique, dynamic sentinel node biopsy, is showing its predictive value in intermediate- and high-risk patients and is advisable (grade B recommendation)
3.	If nodes are palpable, it is mandatory to record nodal morphological and physical characteristics and to perform a histological diagnosis (grade B recommendation)
Distant metastasis (only in patients with metastatic inguinal nodes) (grade B recommendation)	
1.	A pelvic/abdominal CT scan (positive pelvic nodes) is advisable
2.	A chest radiography is also advisable
3.	Routine laboratory determinations are optional for specific conditions
4.	A bone scan is only recommended in symptomatic cases

4.5 REFERENCES

1. Solsona E, Iborra I, Rubio J, Casanova JL, Ricos JV, Calabuig C. Prospective validation of the association of local tumor stage grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. J Urol 2001;165:1506-1509. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11342906&dopt=Abstract
2. Agrawal A, Pai D, Ananthakrishnan N, Smile SR, Ratnakar C. Clinical and sonographic findings in carcinoma of the penis. J Clin Ultrasound 2000;28:399-406. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10993967&dopt=Abstract
3. Lont AP, Besnard AP, Gallee MP, van Tinteren H, Horenblas S. A comparison of physical examination and imaging in determining the extent of primary penile carcinoma. BJU Int 2003;91:493-495. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12656901&dopt=Abstract

4. Horenblas S. The accuracy of ultrasound in squamous cell carcinoma. In: *The Management of Penile Squamous Cell Carcinoma. A Retrospective and Prospective Study*. Thesis. Amsterdam Zoetermeer: BV Export drukkerij, 1993, pp. 71-83.
5. Cabanas RM. An approach for the treatment of penile carcinoma. Cancer 1977;39:456-466. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=837331&dopt=Abstract
6. Pettaway CA, Pisters LL, Dinney CPN, Jularbal F, Swanson DA, von Eschenbach AC, Ayala A. Sentinel lymph node dissection for penile carcinoma: the M.D. Anderson Cancer Center Experience. J Urol 1995;154:1999-2003. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7500444&dopt=Abstract
7. Horenblas S. Surgical management of carcinoma of the penis and scrotum. In: *Medical Radiology. Diagnostic Imaging and Radiation Oncology*. *Carcinoma of the Kidney and Testis, and Rare Urologic Malignancies*. Petrovich Z, Baert L, Brady LW (eds.) Berlin: Springer-Verlag, 1999, pp. 341-354.
8. Pettaway CA, Jularbal FA, Babaian RJ, Dinney CPN, Pisters LL. Intraoperative lymphatic mapping to detect inguinal metastases in penile carcinoma: results of a pilot study. J Urol 1999;161:159 (abstract 612).
9. Akduman B, Fleshner NE, Ehrlich L, Klotz L. Early experience in intermediate-risk penile cancer with sentinel node identification using the gamma probe. Urology 2001;58:65-68. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11445481&dopt=Abstract
10. Perdona S, Gallo L, Claudio L, Marra L, Gentile M, Gallo A. Role of crural inguinal lymphadenectomy and dynamic sentinel lymph node biopsy in lymph node staging in squamous-cell carcinoma of the penis. Our experience. Tumori 2003;89(Suppl):276-279. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12903620&dopt=Abstract
11. Tanis PJ, Lont AP, Meinhardt W, Olmos RA, Nieweg OE, Horenblas S. Dynamic sentinel node biopsy for penile cancer: reliability of a staging technique. J Urol 2002;168:76-80. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12050496&dopt=Abstract
12. Warwoschek F, Vogt H, Bachter D, Weckermann D, Hamm M, Harzmann R. First experience with gamma probe guided sentinel lymph node surgery in penile cancer. Urol Res 2000;28:246-249. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11011963&dopt=Abstract
13. Lont AP, Horenblas S, Tanis PJ, Gallee MP, Van Tinteren H, Nieweg OE. Management of clinically node negative penile carcinoma: improved survival after the introduction of dynamic sentinel node biopsy. J Urol 2003;170:783-786. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12913697&dopt=Abstract
14. Horenblas S, Van Tinteren H, Delamarre JFM, Moonen LM, Lustig V, van Waardenburg EW. Squamous cell carcinoma of the penis. III. Treatment of regional lymph nodes. J Urol 1993;149:492-497. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8437253&dopt=Abstract
15. Ornellas AA, Seixas ALC, Marota A, Wisnescky A, Campos F, de Moraes JR. Surgical treatment of invasive squamous cell carcinoma of the penis: retrospective analysis of 350 cases. J Urol 1994;151:1244-1249. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7512656&dopt=Abstract
16. Pizzocaro G, Piva L, Nicolai N. Treatment of lymphatic metastasis of squamous cell carcinoma of the penis: experience at the National Tumor Institute of Milan. Arch Ital Urol Androl 1996;68:169-172. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8767505&dopt=Abstract
17. Senthil Kumar MP, Ananthakrishnan N, Prema V. Predicting regional node metastasis in carcinoma of the penis: a comparison between fine-needle aspiration cytology, sentinel lymph node biopsy and medial inguinal lymph node biopsy. BJU 1998;81:453-457. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9523669&dopt=Abstract

18. Skoog I, Collins BT, Tani E, Ramos RR. Fine-needle aspiration cytology of penile tumors. Acta Cytol 1998;42:1336-1340. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9850639&dopt=Abstract
19. Ravizzini GC, Wagner M, Borges-Neto S. Positron emission tomography detection of metastatic penile squamous cell carcinoma. J Urol 2001;165:1633-1634. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11342941&dopt=Abstract
20. Burgers JK, Badalament RA, Drago JR. Penile cancer: clinical presentation, diagnosis and staging. Urol Clin North Am 1992;19:247-256. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1574815&dopt=Abstract
21. Horenblas S, Van Tinteren H, Delamarre JFM, Moonen LM, Lustig V, van Waardenburg EW. Squamous cell carcinoma of the penis. III. Treatment of regional lymph nodes. J Urol 1993;149:492-497. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8437253&dopt=Abstract
22. Horenbas S, Van Tinteren H, Delemarre JFM, Moonen LM, Lustig V, Kroger R. Squamous cell carcinoma of the penis: accuracy of tumor, nodes and metastasis classification system, and role of lymphangiography, computed tomography scan and fine needle aspiration cytology. J Urol 1991;146:1279-1283. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1942279&dopt=Abstract
23. Lopes A, Bezerra AL, Serrano SV, Hidalgo GS. Iliac nodal metastases from carcinoma of the penis treated surgically. BJU Int 2000;86:690-693. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11069378&dopt=Abstract
24. Srinivas V, Morse M, Herr E, Sogani P, Whitmore WF Jr. Penile cancer: relation of extent of nodal metastasis to survival. J Urol 1987;137:880-882. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3573181&dopt=Abstract
25. Dexeus FH, Logothetis CJ, Sella A, Amato R, Kilbourn R, Fitz K, Striegel A. Combination chemotherapy with methotrexate, bleomycin and cisplatin for advanced squamous cell carcinoma of the male genital tract. J Urol 1991;146:1284-1287. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1719241&dopt=Abstract
26. Montie JE. Follow-up after penectomy for penile carcinoma. Urol Clin North Am 1994;21:725-727. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7974900&dopt=Abstract

5. TREATMENT

5.1 Primary lesion

5.1.1 Penile intraepithelial neoplasia

In cases of penile intraepithelial neoplasia, a penis-preserving strategy is strongly recommended.

The following therapies have been used successfully (1,2) (level of evidence: 3):

- laser therapy (carbon dioxide (CO_2)-laser or Neodynium:Yttrium-Aluminum-Garnet: Nd-YAG)
- cryotherapy
- photodynamic therapy
- topical imiquimod, 5%
- 5-fluorouracil (5-FU) cream
- local excision
- Mohs' surgery.

The therapeutic approach should be decided according to the preferences of the surgeon and patient and available technology.

5.1.2 Category Ta-1G1-2

For patients who can guarantee regular follow-up, a penis-preserving strategy is strongly recommended, i.e. laser therapy (3-7), local excision plus reconstructive surgery (8-10), radiotherapy or brachytherapy (11-16), glansectomy (10,17) (level of evidence: 2a). With radiotherapy and laser therapy, the organ-preserving rate is 55-84%.

There is no difference in the local recurrence rates (15-25%) between micrographic surgery, external radiation therapy, interstitial brachytherapy and laser therapy. However, with traditional conservative surgery, the recurrence rate is more variable at 11-50% (10). A pathological assessment of surgical margins is essential in applying these procedures and to reduce the rate of local recurrence to 9-24% (9,18,19) (level of evidence: 2b). Meticulous follow-up is essential so that local disease recurrences can be treated as soon as possible. Generally, a local recurrence need not have a negative impact on survival (12,20) (level of evidence: 3). In patients who do not comply with regular follow-up, partial amputation is an optional recommendation.

5.1.3 Category T1G3, T≥2

Partial or total amputation, or emasculation according to tumour extent, can be considered to be standard therapies (2,10,21,22) (level of evidence: 2a).

A conservative strategy is an alternative in very carefully selected patients with tumours encompassing less than half of the glans and in whom a close follow-up can be carried out (17,23) (level of evidence: 2b).

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 (12,24-26) (level of evidence: 3).

5.1.4 Local disease recurrence

For local recurrence after conservative therapy, a second conservative procedure is strongly advised if there is no corpora cavernosa invasion (7,20) (level of evidence: 2b). However, if there is a large or a deep infiltrating recurrence, partial or total amputation is strongly recommended.

5.1.5 Radiotherapy

External beam irradiation or brachytherapy can ensure excellent results in infiltrating tumours less than 4 cm in diameter. Late sequelae (e.g. meatal stenosis, skin necrosis) are not uncommon. The use of a single technique achieves better results than combined external beam irradiation and brachytherapy (11-16) (level of evidence: 2a).

5.2 Regional nodes

In penile carcinoma, the success of therapy is related to lymph node status and treatment. Lymphadenectomy is an effective therapy for patients with positive lymph nodes (21,22,27-29) (level of evidence: 2a). However, this procedure is associated with a high morbidity rate of 30-50% (2,30), even with modern technical modifications (31-33). This morbidity precludes its prophylactic use, although some controversy still surrounds this aspect (1,34). The rational use of lymphadenectomy requires a careful groin assessment and an awareness of predictive factors for positive lymph nodes (35-37).

5.2.1 Non-palpable nodes

Analysis (uni- and multivariate) of prognostic factors has identified three risk groups for developing nodal metastases (2,4,38,39) (level of evidence: 2a).

Low-risk group: In patients at low risk of developing nodal micrometastases (pTis, pTaG1-2 or pT1G1), a surveillance programme is strongly advised because the probability of occult micrometastases occurring in inguinal lymph nodes is less than 16.5% (38-40) (level of evidence: 2a). If patients are considered unreliable for follow-up, a ‘modified’ inguinal lymphadenectomy is an optional recommendation.

Intermediate-risk group: In cases of intermediate risk (T1G2), therapeutic decision-making should take into account vascular or lymphatic invasion and growth pattern (35-37) (level of evidence: 2a).

In patients with no vascular or lymphatic invasion, or a superficial growth pattern on the primary tumour, a surveillance programme is mandatory. However, modified lymphadenectomy is strongly recommended in cases of vascular or lymphatic involvement or of infiltrating growth pattern, unless patients can reliably receive regular follow-up. The current high reliability of dynamic sentinel node biopsy demonstrated in recent reports (41) (level of evidence: 2a) can replace the use of predictive factors in indicating the need for modified lymphadenectomy in this risk group.

High-risk group: In patients at high risk of nodal involvement (T (2 or G3), modified or radical inguinal lymphadenectomy is strongly recommended. In these patients, the incidence of occult metastases ranges between 68% and 73% (4,38-40) (level of evidence: 2a).

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

5.2.2 Palpable nodes with positive histopathology

Positive palpable nodes: Bilateral radical inguinal lymphadenectomy is strongly recommended in cases of positive palpable nodes.

There is great controversy about when to perform pelvic lymphadenectomy. Immediate or delayed pelvic lymphadenectomy can be performed in cases where two or more positive inguinal lymph nodes or extracapsular invasion are found upon frozen section biopsies or standard pathology examination. In these cases, the incidence of positive pelvic nodes increases up to 30% (28) (level of evidence: 2b).

Overall, the probability of pelvic lymph nodes is 23% when 2-3 inguinal nodes are involved and 56% when more than 3 nodes are involved (42) (level of evidence: 2b). In these cases, metastases are often microscopic and offer the possibility of cure in 14-54% (28,43) (level of evidence: 2b).

In the contralateral inguinal area with no palpable nodes modified, lymphadenectomy can be considered initially and may be extended if positive nodes are present in frozen section biopsies.

Fixed inguinal masses or clinically positive pelvic nodes (CT scan or MRI): For patients with fixed inguinal masses or clinically positive pelvic nodes (CT scan or MRI), induction courses of chemotherapy can provide partial or complete clinical responses in 21-60% (35,42-51) (level of evidence: 2b). Subsequent radical ilio-inguinal lymphadenectomy is strongly recommended (4,34,42,44,51) (level of evidence: 2b). However, this strategy should be used as part of a clinical trial.

Another strategy is to use pre-operative radiotherapy (52-54), but the increased morbidity of lymphadenectomy after radiotherapy should be taken into account (22) (level of evidence: 3). Nevertheless, this approach is known to be beneficial with other types of cancer, e.g. rectal and SCC of head and neck regions.

Appearance of inguinal palpable nodes during follow-up: When inguinal palpable nodes appear during a surveillance programme, two treatments are strongly recommended.

- The first treatment is bilateral radical inguinal lymphadenectomy following similar criteria to that discussed above.
- The second treatment is inguinal lymphadenectomy, performed at the site of positive nodes, in the case of a long disease-free interval. The development of positive nodes in both inguinal areas after surveillance should appear synchronously, or within a very short interval in both inguinal areas. The probability of developing subsequent late lymph node metastases in the contralateral inguinal area after initial unilateral inguinal lymph-node recurrence is approximately 10% (55) (level of evidence: 3). Unilateral lymphadenectomy could be warranted in these cases, 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 (29) (level of evidence: 3).

  Adjuvant therapy is advised when there are two or more positive nodes or extracapsular nodal involvement upon pathological examination, as these patients have a poorer prognosis than patients with a single positive lymph node (51-58) (level of evidence: 2a). The results of phase II trials suggest that adjuvant chemotherapy is beneficial for these patients (51,56-58) (level of evidence: 2b). However, these adjuvant programmes should be performed as part of controlled clinical trials. Fewer data are available on adjuvant radiotherapy (52,54) (level of evidence: 3).

5.3 GUIDELINES ON TREATMENT OF PENILE CARCINOMA

5.3.1 Recommendations for therapy of primary lesion

Penile intraepithelial neoplasia

- Penis-preserving strategy is strongly recommended (grade B recommendation)

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 (grade B recommendation)

Category T1G3, T≥2

- Partial or total amputation or emasculation according to tumour extent can be considered as standard therapy (grade B recommendation)
- Conservative therapies in very carefully selected patients (grade B recommendation)
- Chemotherapy followed by conservative procedures is an investigational option (grade C recommendation)

Local disease recurrence following conservative therapy

- A second conservative procedure is strongly advised if there is no corpora cavernosa invasion (grade B recommendation)
- If there is a large or infiltrating recurrence, partial or total amputation is strongly recommended (grade B recommendation)

5.3.2 Recommendations for regional node therapy if non-palpable nodes

Low risk of occult metastases (pTis, pTaG1-2, pT1G1)

- Surveillance programme is strongly advised.
- For patients considered unreliable for surveillance, modified lymphadenectomy is an optional recommendation (grade B recommendation)

High risk of occult metastases (pT≥2 or G3)

- Modified or radical lymphadenectomy is strongly recommended (grade B recommendation)

Intermediate risk of occult metastases (pT1G2)

- Therapeutic decision-making can be aided by considering the vascular or lymphatic invasion and growth pattern (grade B recommendation)
- Strict surveillance is an option in patients without such findings and suitable for reliable and regular follow-up (grade B recommendation)
- Modified lymphadenectomy is an option in patients with poor histological findings (grade B recommendation)
- A dynamic sentinel lymph node biopsy with isosulphan blue or/and ^{99m}Tc-colloid sulphur is an alternative method for indicating lymphadenectomy when technology is available
- Modified lymphadenectomy can be enlarged to a radical lymphadenectomy if positive nodes are present (grade B recommendation)

5.3.3 Recommendations for regional node therapy if palpable pathological positive nodes

- Bilateral radical inguinal lymphadenectomy is the standard recommendation (grade B recommendation)
- Pelvic lymphadenectomy could be performed in cases with at least two positive inguinal nodes or extracapsular invasion (grade B recommendation)
- Modified lymphadenectomy can initially be considered on the contralateral inguinal area with no palpable nodes (grade B recommendation)
- Patients with fixed inguinal masses or clinically positive pelvic nodes (CT or MRI) are good candidates for induction chemotherapy followed by radical ilio-inguinal lymphadenectomy (grade B recommendation).
  Another strategy is to use pre-operative radiotherapy, but this has possible harmful complications (grade C recommendation)
- When inguinal palpable nodes appear during a surveillance programme, there are two possible recommendations:
  - bilateral radical inguinal lymphadenectomy
  - inguinal lymphadenectomy at the site of positive nodes, according to the disease-free interval and if less than two positive lymph nodes were found on the specimen (grade B recommendation).

  Adjuvant chemotherapy is an advisable recommendation when there are at least two positive nodes or extracapsular nodal involvement; another option is adjuvant radiotherapy (grade C recommendation)

5.4 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 can be administered first. Radical or palliative surgery or radiotherapy is indicated according to the tumour response.

5.5 Distant metastases

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

5.6 Quality of life

Although penile carcinoma is a malignant disease with a high probability of cure, it has a high degree of therapeutic morbidity.

There is no consensus regarding the impact of partial penectomy on quality of life, probably because of the different patient attitudes in Europe and South America (59). However, a negative impact has been observed in Europe on general health, anxiety, social problems and sexual function domains (60-62) (level of evidence: 2a).

With regard to quality of life, the therapeutic decision-making process should take into account the patient's age, performance status, socio-economic factors and geographical location, sexual function, patient motivation and psychological condition, the morbidity of different procedures and tumour biology.

5.7 Technical aspects

5.7.1 Primary lesion

The most important factors in the choice of conservative strategy are the simplicity and morbidity of the procedures and the surgeon's experience. Formal circumcision is mandatory before brachytherapy.

5.7.2 Partial amputation

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 margins with pathological confirmation. A surgical margin of 10 mm would be safe (63); this should be 1.5 cm for G3 (64) (level of evidence: 2b).

5.7.3 Radical inguinal lymphadenectomy

Radical inguinal lymphadenectomy should include the following anatomical landmarks: inguinal ligament, adductor muscle, sartorius muscle with the femoral vein and artery as floor of dissection.

5.7.4 'Modified' inguinal lymphadenectomy

The saphenous vein should be preserved and there should be 1-2 cm reduction of the lateral and inferior boundaries. With these modifications, it is a safe procedure, with complications and morbidity rates lower than radical ilio-inguinal lymphadenectomy (31-34) (level of evidence: 2b).

5.7.5 Lymphadenectomy

Morbidity from lymphadenectomy for penile cancer remains high, despite improvements in surgical techniques, including:

- thicker and less extensive skin flaps to reduce skin necrosis
- femoral vessels protected by coverage with the sartorius muscle
- improved lymphatic control and preservation of the saphenous vein to decrease leg oedema
- anticoagulation both during and after surgery to prevent deep venous thrombosis and pulmonary embolism.

At the MD Anderson Cancer Center, prophylactic and therapeutic dissections were associated with a lower incidence of complications compared with palliative dissections, and major complications were more frequent in the palliative group (30).

5.7.6 Pelvic lymphadenectomy

Pelvic lymphadenectomy includes the external iliac lymphatic chain and ilio-obturator chain with the following borders:

- proximal boundary: iliac bifurcation
- lateral boundary: ilio-inguinal nerve
- medial boundary: obturator nerve.

5.8 Chemotherapy

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

5.8.1 Adjuvant chemotherapy

Adjuvant chemotherapy with two courses of cisplatin and 5-FU may be sufficient or vincristine, methotrexate and bleomycin may be administered once a week for 12 weeks on an out-patient basis (57). This regimen following radical resection of lymph-node metastases achieved 82% 5-year survival in 25 consecutive patients as compared to only 37% in 31 consecutive historical controls treated with radical surgery alone (57). A more accurate analysis of two series allowed identification of interesting risk factors: none of the category pN1 patients relapsed, independently of adjuvant or no adjuvant chemotherapy; and relapses occurred after adjuvant chemotherapy (50%) only in patients with bilateral and/or pelvic metastases (51,58,65) (level of evidence: 2b).

5.8.2 Neoadjuvant chemotherapy for fixed inguinal nodes

Induction chemotherapy comprised of three to four courses of cisplatin and 5-FU with appropriate doses and sequence. In Pizzocaro's series (51,57), among 16 patients treated with neoadjuvant chemotherapy for fixed inguinal nodes, 9 (56%) of the 16 patients could be radically resected following primary chemotherapy, and 5 (31%) have probably been cured. The authors observed that cisplatin plus 5-FU achieved the best results. This was also corroborated by a compilation of 29 patients with similar characteristics, with a clinical response rate of 66%. Radical rescue surgery was performed in 38% of patients. 17% were probably cured (46,48,65,66) (level of evidence: 2b). Overall, when combining all reported series, the response rate was 68.5%, radical surgery rate was 42.8% and survival rate was 23% (42,50).

5.8.3 Chemotherapy for advanced disease

Chemotherapy for advanced disease has not been widely used in penile cancer. The most commonly used combinations are cisplatin and 5-FU (48,65) and cisplatin, bleomycin and methotrexate (46,47). Kattan et al. (66) used several cisplatin-based chemotherapy combinations. Results in patients with widespread disease are usually modest, with 32% complete and partial response rate and 12% treatment-related deaths in the most recent study (47). The response rate is similar in patients treated with cisplatin plus 5-FU, but tolerability of this regimen is much better with no treatment-related deaths (48,65). Intra-arterial chemotherapy in locally advanced or recurrent SCC of the penis is promising (49,67), both as palliative treatment and neoadjuvant therapy.

5.9 Radiotherapy

5.9.1 Primary tumour

External beam radiotherapy or brachytherapy have produced a complete response rate of 56% and 70%, respectively. Although local failure rates were 40% and 16%, respectively, salvage surgical resection can restore local control. A comparison of these methods is difficult because of selection bias due to the exclusion of patients with large volume disease (> 4 cm) from radiotherapy. 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 (42).

5.9.2 Prophylactic radiotherapy

Prophylactic radiotherapy in clinically negative lymph nodes is not recommended because radiotherapy fails to prevent the development of metastatic lymph nodes (53,54). Furthermore, all patients will be exposed to the complications of radiotherapy (22,29) and patient follow-up is more difficult due to radiation-related fibrotic changes, which make physical examination unreliable. There seems to be no role for radiotherapy as a primary treatment in patients with pathological nodes, since the 5-year survival rate with radiotherapy is half the 5-year survival rate obtained with surgery (29).

5.9.3 Pre-operative radiotherapy

Pre-operative radiotherapy in patients with fixed nodes can render them operable but it is unknown whether the fixation is caused by inflammatory reactions or by cancerous growth (22,29,54). More recently, reports have suggested that this strategy should possibly be replaced by chemotherapy (4).

5.9.4 Adjuvant radiotherapy

Adjuvant radiotherapy in cases of metastastic nodes may be used to reduce local recurrence (8,14). A therapeutic schedule for penile cancer is shown in Table 7.

Table 7: Therapeutic schedule for penile cancer

Lesion therapy	Therapy	Recommendations		
		Strong	**Optional**	**Investigational**
Primary tumour	Conservative therapy	Primary/recurrent Tis, Ta-1G1-2	T1G3, T 2 limited to < 50% of glans (fit patients for surveillance)	After chemotherapy, according to tumour response
	Total/partial amputation	Primary/recurrent T1G3, T ≥ 2	Primary or recurrent Ta-1G1-2 (conservative therapy not feasible)	
	Radiotherapy	T1-2 < 4cm	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[1]	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 (patients unfit for follow-up)	
Regional (palpable nodes)	Radical LND[2]	Positive nodes at presentation Positive nodes after surveillance	Plus adjuvant chemotherapy[3] or radiotherapy[4] (> 1 positive node) Unilateral LND on nodal site (disease-free interval > 6 months and < 3 positive nodes)	
	Chemotherapy[3] +/- LND	Fixed inguinal masses, pelvic nodes (fit patients for chemotherapy)		
	Radiotherapy[4] +/- LND		Fixed masses (patients unfit for chemotherapy)	
Distant metastases			Chemotherapy[3] or palliative therapy (according to performance status, age, etc.)	

LND = lymphadenectomy.

1 *Modified LND can be extended to radical in cases where there are positive nodes.*

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

3 *Chemotherapy should be discussed with medical oncologist and preferably be given in the context of clinical trials.*

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

5.10 REFERENCES

1. Mobilio G, Ficarra V. Genital treatment of penile carcinoma. Curr Opin Urol 2001;11:299-304. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11371784&dopt=Abstract

2. Stancik I, Holtl W. Penile cancer: review of the recent literature. Curr Opin Urol 2003;13:467-472. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14560140&dopt=Abstract
3. Frimberger D, Hungerhuber E, Zaak D, Waidelich R, Hofstetter A, Schneede P. Penile carcinoma. Is Nd: YAG laser therapy radical enough? J Urol 2002;168:2418-2421. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12441930&dopt=Abstract
4. Pizzocaro G, Piva L, Bandieramonte G, Tana S. Up-to-date management of carcinoma of the penis. Eur Urol 1997;32:5-15. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9266225&dopt=Abstract
5. Van Bezooijen BP, Horenblas S, Meinhardt W, Newling DW. Laser therapy for carcinoma in situ of the penis. J Urol 2001;166:1670-1671. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11586199&dopt=Abstract
6. Windahl T, Hellsten S. Laser treatment of localized squamous cell carcinoma of the penis. J Urol 1995;154:1020-1023. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7637046&dopt=Abstract
7. Windalh T, Andersson S-O. Combined laser treatment for penile carcinoma: results after long-term follow up. J Urol 2003;169:2118-2121. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12771731&dopt=Abstract
8. Banon Perez VJ, Nicolas Torralba JA, Valdevira Nadal P, Server Pastor G, Garcia Hernandez JA, Guardiola Mas A, Gomez Gomez G, Prieto Gonzalez A, Martinez Barba E, Perez Albacete M. Squamous carcinoma of the penis. Arch Esp Urol 2000;53:693-699. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11126970&dopt=Abstract
9. Bissada NK, Yakout HH, Fahmy WE, Gayed MS, Touijer AK, Greene GF, Hanash KA. Multi-institutional long-term experience with conservative surgery for invasive penile carcinoma. J Urol 2003;169:500-502. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12544296&dopt=Abstract
10. Ficarra V, Maffei N, Piacentine I, Al Rabi N, Cerruto MA, Artibani W. Local treatment of penile squamous cell carcinoma. Urol Int 2002;69:169-173. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12372882&dopt=Abstract
11. Crook J, Grimard L, Tsihlias J, Morash C, Panzarella T. Interstitial brachytherapy for penile cancer: an alternative to amputation. J Urol 2002;167:506-511. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11792907&dopt=Abstract
12. Gotsadze D, Matveev, B, Zak, B, Mamaladze V. Is conservative organ-sparing treatment of penile carcinoma justified? Eur Urol 2000;38:306-312. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10940705&dopt=Abstract
13. Kiltie AE, Elwell C, Close HJ, Ash DV. Iridium-192 implantation for node-negative carcinoma of the penis: the Cookridge Hospital experience. Clin Oncol 2000;12:25-31. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10749016&dopt=Abstract
14. Mahlmann B, Doehn C, Feyerabend T. (Radiochemotherapy of penis carcinoma.) Urologie A 2001;40:308-312. [German] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11490865&dopt=Abstract
15. Rozan H, Albuisson E, Giraud B, Donnarieix D, Delannes M, Pigneux J, Hoffstetter S, Gerbaulet A, Chinet-Charrot P, Goupil A et al. Interstitial brachytherapy for penile carcinoma: a multicentric survey (259 patients). Radiother Oncol 1995;36:83-93. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7501816&dopt=Abstract

16. Zouhair A, Coucke PA, Jeanneret W, Douglas P, Do HP, Jichlinski P, Mirimanoff RO, Ozsahin M. Radiation therapy alone or combined surgery and radiation therapy in squamous-cell carcinoma of the penis? Eur J Cancer 2001;37:198-203. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11166146&dopt=Abstract
17. Hatzichristou DG, Apostolidis A, Tzortzis V, Hatzimouratidis K, Ioannides E, Yannakoyorgos K. Glansectomy: an alternative surgical treatment for Buschke-Lowenstein tumors of the penis. Urology 2001;57:966-969. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11337304&dopt=Abstract
18. Davis JW, Schellhammer PF, Schlossberg SM. Conservative surgical therapy for penile and urethral carcinoma. Urology 1999;53:386-392. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9933060&dopt=Abstract
19. Mohs FE, Snow SN, Larson PO. Mohs micrographic surgery for penile tumors. Urol Clin North Am 1992;19:291-304. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1574820&dopt=Abstract
20. Koch MO, Smith JA Jr. Local recurrence of squamous cell carcinoma of the penis. Urol Clin North Am 1994;21:739-743. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7974902&dopt=Abstract
21. Hakenberg OW, Wirth MP. Issues in the treatment of penile carcinoma. A short review. Urol Int 1999;62:229-233. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10567890&dopt=Abstract
22. Saint F, Legeais D, Leroy X, Biserte J, Gosselin B, Mazeman E. (Therapeutic management of epidermoid carcinoma of the penis: anatomoclinical discussion and review of the literature.) Prog Urol 2000;10:128-133. [French] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10785933&dopt=Abstract
23. Horenblas S, Van Tinteren H, Delemarre JFM, Boon TA, Moonen LMF, Lustig V. Squamous cell carcinoma of the penis. II. Treatment of the primary tumor. J Urol 1992;147:1533-1538. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1593683&dopt=Abstract
24. Doehn C, Feyerabend T. Radiochemotherapy of penis carcinoma. Urology 2001;40:313-314. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11490866&dopt=Abstract
25. Shirahama T, Takemoto M, Nishiyama K, Nobori T, Kawahara M, Ohyama M, Ohi Y. A new treatment for penile conservation in penile carcinoma: a preliminary study of combined laser hyperthermia, radiation and chemotherapy. Br J Urol 1998;82:687-693. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9839584&dopt=Abstract
26. Eisenberger MA. Chemotherapy for carcinoma of the penis and urethra. Urol Clin North Am 1992;19:333-338. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1374199&dopt=Abstract
27. Kamat MR, Kulkarni JN, Tongaonkar HB. Carcinoma of the penis: the Indian experience. J Surg Oncol 1993;52:50-55. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8441263&dopt=Abstract
28. Ornellas AA, Seixas ALC, Marota A, Wisnescky A, Campos F, de Moraes JR. Surgical treatment of invasive squamous cell carcinoma of the penis: retrospective analysis of 350 cases. J Urol 1994;151:1244-1249. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7512656&dopt=Abstract
29. Horenblas S. Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: the role and technique of lymph node dissection. BJU Int 2001;88:473-483. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11589660&dopt=Abstract

30. Bevan-Thomas R, Slaton JW, Pettaway CA. Contemporary morbidity from lymphadenectomy for penile squamous cell carcinoma: the M.D. Anderson Cancer Center Experience. J Urol 2002;167:1638-1642. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11912379&dopt=Abstract
31. Coblentz TR, Theodorescu D. Morbidity of modified prophylactic inguinal lymphadenectomy for squamous cell carcinoma of the penis. J Urol 2002;168:1386-1389. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12352399&dopt=Abstract
32. Colberg JW, Andriole GL, Catalona WJ. Long-term follow-up of men undergoing modified inguinal lymphadenectomy for carcinoma of the penis. BJU 1997;79:54-57. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9043497&dopt=Abstract
33. Jacobellis U. Modified radical inguinal lymphadenectomy for carcinoma of the penis: technique and results. J Urol 2003;169:1349-1352. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12629358&dopt=Abstract
34. Wilbert DM. (Lymph node metastases in penis carcinoma. Therapeutic options and outcome.) Urologe A 1999;38:332-336. [German] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10444790&dopt=Abstract
35. Ficarra V, Martignoni G, Maffei N, Cerruto MA, Novara G, Cavalleri S, Artibani W. Predictive pathological factors of lymph nodes involvement in the squamous cell carcinoma of the penis. Int Urol Nephrol 2002;34:245-250. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12775105&dopt=Abstract
36. Lopes A, Hidalgo GS, Kowallski LP, Torloni H, Rossi BM, Fonseca FP. Prognostic factors in carcinoma of the penis: multivariate analysis of 145 patients treated with amputation and lymphadenectomy. J Urol 1996;156:1637-1642. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8863559&dopt=Abstract
37. Slaton JW, Morgenstern N, Levy DA, Santos MW Jr, Tamboli P, Ro JY, Ayala AG, Pettaway CA. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal lymph node metastasis in penile squamous cancer. J Urol 2001;165: 1138-1142. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11257655&dopt=Abstract
38. Solsona E, Iborra I, Rubio J, Casanova JL, Ricos JV, Calabuig C Prospective validation of the association of local tumor stage and grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. J Urol 2001;165:1506-1509. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11342906&dopt=Abstract
39. Horenblas S, Van Tinteren HV. Squamous cell carcinoma of the penis. IV. Prognostic factors of survival: analysis of tumor, nodes and metastasis classification system. J Urol 1994;151:1239-1243. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8158767&dopt=Abstract
40. Theodorescu D, Russo P, Zhang ZF, Morash C, Fair WF. Outcomes of initial surveillance of invasive squamous cell carcinoma of the penis and negative nodes. J Urol 1996;155:1626-1631. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8627839&dopt=Abstract
41. Lont AP, Horenblas S, Tanis PJ, Gallee MP, van Tinteren H, Nieweg OE. Management of clinically node negative penile carcinoma: improved survival after the introduction of dynamic sentinel node biopsy. J Urol 2003;170:783-786. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12913697&dopt=Abstract
42. Culkin DJ, Beer TM. Advanced penile carcinoma. J Urol 2003;170:359-365. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12853775&dopt=Abstract

43. Lopes A, Bezerra AL, Serrano SV, Hidalgo GS. Iliac nodal metastases from carcinoma of the penis treated surgically. BJU Int 2000;86:690-693. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11069378&dopt=Abstract
44. Fisher HA, Barada JH, Horton J. Neoadjuvant therapy with cisplatin and 5-fluorouracil for stage III squamous cell carcinoma of the penis. Acta Oncol 1990;27A-653 (abstract 352A).
45. Corral DA, Sella A, Pettaway CA, Amato RJ, Jones DM, Ellerhorst J. Combination chemotherapy for metastatic or locally advanced genitourinary squamous cell carcinoma: a phase II study of methotrexate, cisplatin and bleomycin (MPB). J Urol 1998;160:1770-1774. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9783949&dopt=Abstract
46. Dexeus FH, Logothetis CJ, Sella A, Amato R, Kilbourn R, Fitz K, Striegel A. Combination chemotherapy with methotrexate, bleomycin and cisplatin for advanced squamous cell carcinoma of the male genital tract. J Urol 1991;146:1284-1287. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1719241&dopt=Abstract
47. Haas GP, Blumenstein BA, Gagliano RG, Russell CA, Rivkin SE, Culkin DJ, Wolf M, Crawford ED. Cisplatin, methotrexate and bleomycin for the treatment of carcinoma of the penis: a Southwest Oncology Group Study. J Urol 1999;161:1823-1825. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10332445&dopt=Abstract
48. Hussein AM, Benedetto P, Sridhar KS. Chemotherapy with cisplatin and 5-fluorouracil for penile and urethral squamous cell carcinomas. Cancer 1990;65:433-438. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2297633&dopt=Abstract
49. Huang XY, Kubota Y, Nakada T, Sasagawa I, Suzuki H, Ishigooka M. Intra-arterial infusion chemotherapy for penile carcinoma deep inguinal lymph node metastasis. Urol Int 1999;62:245-248. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10567893&dopt=Abstract
50. Otto T, Suhur J, Krege S, Rübben H. Die therapie des fortgeschitten peniskarzinoms. Urologe A 2003;42:1466-1469. [German] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14624345&dopt=Abstract
51. Pizzocaro G, Piva L, Nicolai N. Improved management of nodal metastases of squamous cell carcinoma of the penis. J Urol 1995;153:246 (abstract 69).
52. Gerbaulet A, Lambin P. Radiation therapy of cancer of the penis. Indications, advantages, and pitfalls. Urol Clin North Am 1992;19:325-332. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1574823&dopt=Abstract
53. Kulkarni JN, Kamat MR. Prophylactic bilateral groin node dissection versus prophylactic radiotherapy and surveillance in patients with N0 and N1-2A carcinoma of the penis. Eur Urol 1994;26:123-128. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7957466&dopt=Abstract
54. Ravi R, Chaturvedt HK, Sastry DV. Role of radiation therapy in the treatment of carcinoma of the penis. Br J Urol 1994;74:646-651. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7530129&dopt=Abstract
55. Fair WR, Perez CA, Anderson T. Cancer of the urethra and penis. In: *Cancer: Principles and Practice of Oncology.* De Vita V, Hellman S, Rosemberg SA (eds.) Philadelphia) (lippincott, 1989, pp. 1063-1070.
56. Horenblas S. Neo-adjuvant and adjuvant treatment in penile squamous cell carcinoma. Acta Urol Belg 1996;64:99-101. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8701826&dopt=Abstract
57. Pizzocaro G, Piva L. Adjuvant and neoadjuvant vincristine, bleomycin and methotrexate for inguinal metastases from squamous cell carcinoma of the penis. Acta Oncol 1988;27:823-824. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2466471&dopt=Abstract

58. Pizzocaro G, Piva L, Nicolai N. Treatment of lymphatic metastasis of squamous cell carcinoma of the penis at the National Tumor Institute of Milan. Arch Ital Urol Androl 1996;68:169-172. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8767505&dopt=Abstract
59. Levy D'Ancona CA, Botega NJ, De Moraes C, Lavoura NS Jr, Santos JK, Rodrigues Netto N Jr. Quality of life after partial penectomy for penile carcinoma. Urology 1997;50:593-596. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9338738&dopt=Abstract
60. Ficarra V, Righetti R, D'Amico A, Pilloni S, Balzarro M, Schiavone D, Malossini G, Mobilio G. General state of health and psychological well-being in patients after surgery for urological malignant neoplasms. Urol Int 2000;65:130-134. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11054029&dopt=Abstract
61. Hadzi-Djokic J, Dzamic Z, Tulic C, Dragicevic D, Janicic A, Durutovic O. Surgical treatment and quality of life in patients with carcinoma of the penis. Acta Chir Iugosl 1999;46(Suppl):7-10. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10951769&dopt=Abstract
62. Opjordsmoen S, Fossa SD. Quality of life in patients treated for penile carcinoma. A follow-up study. Br J Urol 1994;74:652-657. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7827818&dopt=Abstract
63. Hoffman MA, Renshaw AA, Loughlin KR. Squamous cell carcinoma of the penis and microscopic margins: how much margin is needed for local cure? Cancer 1999;85:1565-1568. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10193947&dopt=Abstract
64. Agraval A, Pai D, Ananthakrishamn N, Smile SR, Ratnakar C. The histological extent of the local spread of carcinoma of the penis and its therapeutic implications. BJU Int 2000;85:299-301. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10671885&dopt=Abstract
65. Shammas FV, Ous S, Fossa DS. Cisplatin and 5-fluorouracil in advanced cancer of the penis. J Urol 1992;147:630-632. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1538445&dopt=Abstract
66. Kattan J, Culine S, Droz JP, Fadel E, Court B, Perrin JL, Wibault P, Haie-Meder C. Penile cancer chemotherapy twelve years' experience at Institut Gustave-Roussy. Urology 1993;42:559-562. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7694417&dopt=Abstract
67. Roth AD, Berney CR, Rohner S, Allal AS, Morel P, Marti MC, Aapro MS, Alberto P. Intra-arterial chemotherapy in locally advanced or recurrent carcinomas of the penis and anal canal: an active treatment modality with curative potential. Br J Cancer 2000;83:1637-1642. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11104558&dopt=Abstract

6. FOLLOW-UP

Penile carcinoma is one of the few solid tumours in which lymphadenectomy can provide a high cure rate even when 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 therefore faced with the dilemma of reaching an appropriate balance between decreasing morbidity by using conservative procedures and disease control. In this context, follow-up is crucial in order to achieve similar survival rates to those achieved with early radical surgery. Moreover, most relapses occur during the first 2 years; late recurrences, though uncommon, may occur. As penile carcinoma is associated with poor socio-economic conditions, close surveillance cannot always be performed.

6.1 Why follow-up?

With respect to the primary lesion, the local disease 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%;

with conservative therapies, this might increase to 50% (1). Nevertheless, local recurrence does not have a negative impact on cause-specific survival, provided an early diagnosis is carried out (2,3).

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 (1,4). However, a surveillance programme implies close follow-up as late diagnosis seems to be a negative prognostic factor.

In summary, the potential development of local recurrence and inguinal lymph node metastasis in patients treated with conservative approaches, as well as the possibility of curing patients following the early detection of relapse, justifies the need for follow-up in patients with penile carcinoma.

6.2 How to follow-up

As the penis and inguinal lymph nodes are externally situated areas, 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 compared to pathological examination ranges from 47 to 86% (5,6). Moreover, in patients with initially non-palpable lymph nodes, the development of palpable nodes during follow-up means metastases in 100% of cases.

CT scan and chest radiographs can be additional tests used 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 appropriate 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.

6.3.1 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 local recurrences occur in this period. Long-term follow-up is also recommended every 6 months because late local recurrences have been observed (7). Patient self-evaluation is also advisable and patients should be informed about the possible warning signals. This follow-up schedule is advised because the disease recurrence rate is high and follow-up increases the chance of improving the cure.

For patients treated with partial or total penectomy, a follow-up appointment every 4 months for 2 years, then at 6-monthly intervals for 1 year, and annually thereafter, is recommended. For the latter period, no hard data are available to suggest a specific interval. This schedule is recommended because local disease recurrence, although infrequent, usually occurs very early and an early diagnosis is necessary because of the aggressive behaviour of the tumour (8).

6.3.2 Regional areas

If a surveillance programme has been implemented after removal of the primary tumour, it is recommended that a groin evaluation should be carried out every 2 months for 2 years, then every 3 months during the next year, and then every 6 months for a further 2 years, (9,10). No CT scan and chest radiographs are necessary. The rationale for this scheme is based on the fact that most 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 the number, size and bilateralism of the lymph nodes (11,12). Very close follow-up is therefore advisable.

If inguinal lymphadenectomy has been performed and no tumour has been found upon pathological examination of the specimen, a physical evaluation is recommended every 4 months for 2 years and then every 6 months for the next year; subsequently, it is not completely necessary to carry out 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 as inguinal lymphadenectomy has a high morbidity rate.

If inguinal lymphadenectomy has been performed and positive lymph nodes have been observed upon pathological examination, specific follow-up cannot be recommended because of the many variables involved including:

- number of positive lymph nodes (uni- or bilaterally)
- whether pelvic lymphadenectomy was performed, with or without positive lymph nodes
- type of adjuvant therapy carried out and the scheme used.

In relation to these variables, each institution 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. A quality-of-life assessment should

essentially encompass sexual activity and lymphadenectomy morbidity (lymphoedma). The follow-up schedule is summarized in Table 8.

Table 8: 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+)	Institutional protocol[1]	Institutional protocol[1]	Institutional protocol[1]	Physical/self exam/QOL/CT scan/chest radiograph	Bone scan (symptoms)

LND = lymphadenectomy; QOL = quality of life (physical and sexual); CT = computed tomography.
[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.

6.4 GUIDELINES FOR FOLLOW-UP IN PENILE CANCER

Primary tumour

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

Regional nodes and distant metastasis

- 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 (grade C recommendation)
- 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. After this, it is not mandatory to carry out follow-up (grade C recommendation)
- If inguinal lymphadenectomy was performed (pN1-3), specific follow-up cannot be recommended. Physical examination, CT scan, chest radiography and the appropriate intervals between them should be defined by each institution (grade C recommendation)
- Bone scan and other tests are only recommended in symptomatic patients (grade B recommendation)

6.5 REFERENCES

1. Mobilio G, Ficarra V. Genital treatment of penile carcinoma. Curr Opin Urol 2001;11:299-304. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11371784&dopt=Abstract
2. Gotsadze D, Matveev B, Zak B, Mamaladze V. Is conservative organ-sparing treatment of penile carcinoma justified? Eur Urol 2000;38:306-312. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10940705&dopt=Abstract

3. Koch MO, Smith JA Jr. Local recurrence of squamous cell carcinoma of the penis. Urol Clin North Am 1994;21:739-743. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7974902&dopt=Abstract
4. Wilbert DM. [Lymph node metastases in penis carcinoma. Therapeutic options and outcome.] Urologe A 1999;38:332-336. [German] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10444790&dopt=Abstract
5. Horenblas S, van Tinteren H, Delamarre JFM, Moonen LM, Lustig V, van Waardenburg EW. Squamous cell carcinoma of the penis. III. Treatment of regional lymph nodes. J Urol 1993;149:492-497. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8437253&dopt=Abstract
6. Solsona E, Iborra I, Ricós JV, Monros JL, Dumont R, Casanova J, Calabuig C. Corpus cavernosum invasion and tumor grade in the prediction of lymph node condition in penile carcinoma. Eur Urol 1992;22:115-118. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1478225&dopt=Abstract
7. Horenblas S, Newling DW. Local recurrence tumour after penis-conserving therapy. A plea for long-term follow-up. Br J Urol 1993;72:976-979. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8306171&dopt=Abstract
8. Lerner SE, Jones JG, Fleischmann J. Management of recurrent penile cancer following partial or total penectomy. Urol Clin North Am 1994;21:729-737. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7974901&dopt=Abstract
9. Coblentz TR, Theodorescu D. Morbidity of modified prophylactic inguinal lymphadenectomy for squamous cell carcinoma of the penis. J Urol 2002;168:1386-1389. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12352399&dopt=Abstract
10. Horenblas S. Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: the role and technique of lymph node dissection. BJU Int 2001;88:473-483. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11589660&dopt=Abstract
11. Horenblas S, Van Tinteren HV. Squamous cell carcinoma of the penis. IV. Prognostic factors of survival: analysis of tumor, nodes and metastasis classification system. J Urol 1994;151:1239-1243. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8158767&dopt=Abstract
12. Srinivas V, Morse M, Herr E, Sogani P, Whitmore W Jr. Penile cancer: relation of extent of nodal metastasis to survival. J Urol 1987;137:880-882. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3573181&dopt=Abstract

7. ABBREVIATIONS

This list is not comprehensive for the most common abbreviations

CT	computed tomography
HPV	human papillomavirus
MRI	magnetic resonance imaging
Nd-YAG	Neodynium:Yttrium-Aluminum-Garnet
PET	positron emission tomography
SCC	squamous cell carcinoma
TNM	tumour, node, metastasis
5-FU	5-fluorouracil