Extended lymphadenectomy in penile cancer

Antonio Carlos Lima Pompeo, MD

Division of Urology, University of São Paulo, School of Medicine, São Paulo, Brazil

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Introduction and objective: *There are many controversies regarding the optimal management of the inguinal nodes in patients with penile cancer. The inflammatory response of the draining regional lymph nodes can cause enlargement without implying the presence of metastases. On the other hand, 20% of patients with clinically non-suspicious nodes contain micrometastases. We studied the dissemination risk factors of the primary lesion in penile cancer, the preferential lymphatic pathways, and the extension of lymphadenectomies, in order to understand how to better control this cancer.*

Patients and methods: *In this prospective study of 50 patients (aged 21-73; median age 54) with penile carcinoma, the initial clinical and pathologic findings were compared to biopsy specimens obtained in routine, bilateral, superficial, deep and pelvic lymphadenectomies. Patients were followed from 6 months to 18 years.*

Results: *We found that first, risk factors of tumor spread were primary lesions greater than 2 cm in diameter, unfavorable histology findings, and invasive lesions. Second, these risk factors were present in all patients who had node metastases. Third, clinical staging was not accurate, since there was a tendency to understage 19% of localized disease and overstage 51.5% of metastatic disease. Fourth, the sentinel nodes were the most commonly infiltrated nodes but not present in 2 (11%) of 18 metastatic cases. Fifth, there were no cases of deep inguinal nodes without superficial infiltration. Lastly, there were no cases of pelvic node without prior contamination of inguinal nodes.*

Conclusions: *Ideal candidates for watchful waiting after primary lesion treatment are those who do not have primary lesions greater than 2 cm in diameter, unfavorable histology findings, invasive lesions, or palpable nodes. Performing limited surgery on positive nodes risks leaving some of the tumor. Superficial lymphadenectomy is the procedure of choice in cases of patients with clinical negative nodes and risk factors of tumor spread.*

Key Words: lymphadenectomy in penile cancer, penile cancer dissemination, penile cancer prognostic factors

Introduction

Squamous cell carcinoma of the penis (SCCP) is a rare disease worldwide, but is a significant health problem in some South American and African countries, where it may account for up to 20% of male adult cancers.[1-4] This tumor spreads preferentially by way of the penile lymphatic system to the regional nodes, where metastases are found first in the superficial and deep inguinal nodes, and subsequently in the external iliac and obturator nodes within the pelvis.[4-8] In general, untreated patients die of local complications, mainly sepsis secondary to infections of the ulcerated metastases, or hemorrhagic episodes due to tumor infiltration of the femoral vessels. Distant metastases are seldom found. The extent of involvement of the regional nodes with the tumor is, in fact, the best predictor of long-term survival in patients with SCCP.[9-11] Unlike bladder, prostate, or kidney cancers where metastases to regional lymph nodes can very seldom be treated successfully; SCCP, like testicular cancer, may sometimes be cured by regional lymphadenectomy.[3,12-14]

It is important to point out that about 50% of patients who present with penile cancer have enlarged inguinal nodes. Since infection is often present, differentiation of inflammation due to infection from that due to tumor metastases is frequently challenging, in spite of the use of modern imaging

Address correspondence to R. Iguatemi, 192 / 3º, 01451-010 - São Paulo, SP, Brasil

techniques. Between 30% and 50% of palpable nodes harbor metastatic cancer. More problematic are the 20% of patients with clinically negative groin nodes at diagnosis who have occult metastatic disease which, if not treated, leads to death.

No spontaneous remission of SCCP in patients with this condition has been reported.[2,3,15] It is well known that this cancer presents high resistance to chemotherapy, and radiotherapy with high doses is prone to complications and poor results.[6-26] The surgical approach to groin cancer has two purposes: 1) staging and 2) treatment of the disease that can be achieved mainly in low stages. This therapy, however, has many complications that have been described in the literature and, in a significant number of patients, results in unpleasant side effects such as penile and scrotal lymphedema and substantial edema of the lower limbs. For these reasons, one of the challenges of managing patients with SCCP has been to determine which patients will benefit from inguinal dissection while avoiding unnecessary inguinal lymphadenectomies in those without metastases.[2,11,27-29] The selection of patients to undergo inguinal or even ilioinguinal groin surgery has been an area of debate for a long time. The time of the operation, the extent of the operation — including whether it involves one or both sides — and determining who will benefit, are all controversial subjects.[3,6,15,30-34]

We were prompted to perform this study, since, for the many reasons discussed above, indications for lymphadenectomies remain very controversial. In addition, there is a high incidence of SCCP in Brazil, and a significant number of these patients are referred to our center.

Objectives

We aimed to perform a prospective study of patients with SCCP to compare initial clinical and pathologic findings versus biopsy results of specimens obtained in routine bilateral regional lymphadenectomies, which were performed in all patients regardless the stage of the disease. We sought to first, establish the risk factors for cancer spread; second, study the preferential lymphatic pathways; third, clarify the role of lymphadenectomies in SCCP; and fourth, determine the extent surgery needed for better control of cancer.

Patients and methods

Fifty patients with penile cancer who were referred to our center from 1984 to 1997 were included in this prospective trial. Patient characteristics are summarized in Table 1. After treatment of the primary lesion, the disease was staged clinically and with imaging strategies (US, CT). Routine broad-spectrum antibiotic therapy was administered for 1 month prior to surgery, to diminish the rate of false positive nodes secondary to an inflammatory response. The surgical approach was performed in a staged fashion, so we could separately examine specimens obtained from the different inguinal and pelvic nodes (external and obturator) Figure 1. The limits of the operation were

TABLE 1. **Patient characteristics***

Age range	
21 – 73 years (median, 54 years)	
Ethnicity	
White	32 (64%)
Mixed, black and white	10 (20%)
Black	7 (14%)
Asian	1 (2%)
Clinical stage of penile cancer	
Stage I	16 (32%)
Stage II	6 (12%)
Stage III	24 (48%)
Stage IV	4 (8%)
Squamous cell cancer type	
Undifferentiated	7 (14%)
Moderately differentiated	16 (32%)
Well differentiated	27 (54%)

*Prospective study of 50 penile cancer patients, seen at the Urological Clinic – Hospital das Clínicas center, in São Paulo, Brazil, from 1984 to 1987.

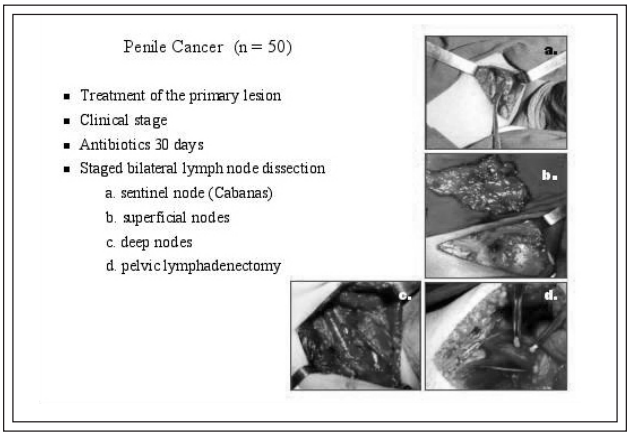

Figure 1. Penile cancer (n = 50) – a) sentinel node; b) superficial nodes; c) deep lymphadenectomy; d) pelvic lymphadenectomy

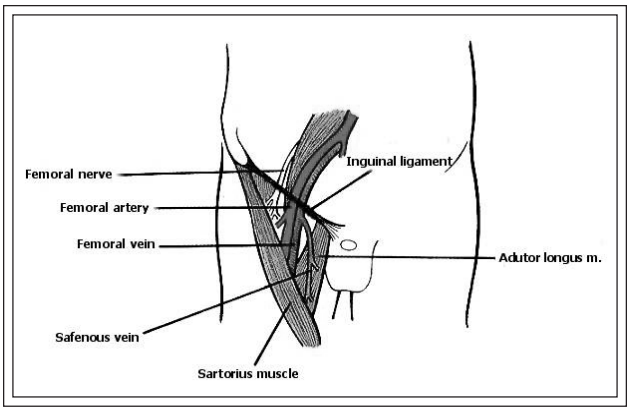

Figure 2. Penile cancer - limits of dissection

cranially the inguinal ligament, laterally the sartorius, medially the adutor longus and inferiorly the junction of these muscles Figure 2. Patients were followed from 6 months to 18 years.

Results

A total of 18 (36%) of the 50 patients had lymph node metastases. There was a tendency to understage the clinical localized disease. A total of 3 (18.7%). of the 16 patients with clinical stage I (T_1) had node involvement. On the other hand, 14 (58.3%) of the 24 clinical stage III patients had localized disease (9 had stage I disease and 5 had stage II disease) Table 2. The characteristics of the primary lesion were significant predictors for spread of cancer. Analysis of the histologically determined cancer size and the extent of invasion showed that small, well-differentiated neoplasias without invasion were associated with localized disease Tables 3, 4, and 5. The study of the lymphatic pathways showed that the sentinel nodes were the most commonly infiltrated, but not in all cases. In 2 (11%) of 18 positive cases, these nodes were negative. The combination of the sentinel plus the other superficial nodes from the different quadrants of the described limits of the operation was present in all metastatic cases Table 6.

In the 6 (12%) of 50 cases of deep metastatic inguinal nodes, there was also infiltration of the superficial nodes. There was no case of deep metastatic node without the presence of superficial localization. Similarly, in 4 (6%) of 50 positive pelvic nodes, there was no infiltration without prior "contamination" of the inguinal lymph nodes.

Our other findings include the fact that there was no significant difference in the direction of cancer spread; it spread to the right side, left side, and both sides, in 24%, 30%, and 24% of cases, respectively. The natural history of the tumor is shown in Figure 3. Surgical complications are summarized in Table 7. The progression rate of the cancer was closely related to the stage of the disease Table 8, to the number of nodes (greater progression with more than 3 nodes), and to the size and shape of the lymph nodes (greater progression with diameter larger than 2 cm, and irregular shape with adherence to surrounding tissues). Similarly, an analysis of survival curves revealed that survival was closely linked to the stage of the disease Figure 4.

TABLE 2. **Clinical stage versus pathologic stage***

	Pathologic stage				
Clinical stage	**I**	**II**	**III**	**IV**	**Total**
	n=21	**n=11**	**n=13**	**n=5**	**n=50**
I	12 (57.14%)	1 (9.09%)	3 (23.08%)	0 (0.00%)	16 (32.00%)
II	0 (0.00%)	4 (36.36%)	2 (15.38%)	9 (0.00%)	6 (12.00%)
III	9 (42.86%)	5 (45.45%)	8 (61.54%)	2 (40.00%)	24 (48.00%)
IV	0 (0.00%)	1 (9.09%)	0 (0.00%)	3 (60.00%)	4 (8.00%)

Concordance: 27/50 = 54%
Discordance: 23/50 = 46%
*in 50 penile cancer patients

TABLE 3. **Histology findings versus pathologic stage***

Histology	**Pathologic stage**				
	I	**II**	**III**	**IV**	**Total**
	n=21	**n=11**	**n=13**	**n=5**	**n=50**
WD	14 (66.67%)	6 (54.55%)	7 (53.85%)	(-)	27 (54%)
MD	6 (28.57%)	4 (36.36%)	4 (30.77%)	2 (40%)	16 (32%)
UD	1 (4.76%)	1 (9.09%)	2 (15.38%)	3 (60%)	7 (14%)

$X^2 = 12.62$, p = 0.0495 (significant)
WD = well differentiated
MD = moderately differentiated
UD = undifferentiated
*in 50 penile cancer patients

TABLE 4. **Invasion versus pathologic stage***

Invasion	**Pathologic stage**				
	I	**II**	**III**	**IV**	**Total**
	n=21	**n=11**	**n=13**	**n=5**	**n = 50**
Yes	9 (42.86%)	7 (63.64%)	11 (84.62%)	5 (100%)	27 (54%)
No	12 (57.14%)	4 (36.36%)	2 (15.38%)	(-)	18 (36%)

$X^2 = 9.28$, p = 0.0257 (significant)
*in 50 penile cancer patients

TABLE 5. **Tumor size versus pathologic stage***

Tumor size	**Pathologic stage**				
	I	**II**	**III**	**IV**	**Total**
	n=21	**n=11**	**n=13**	**n=5**	**n = 50**
>2 cm	5 (23.81%)	2 (18.18%)	2 (15.38%)	(-)	9 (18%)
2 cm – 5 cm	14 (66.67%)	7 (63.64%)	7 (53.85%)	2 (40%)	30 (60%)
>5 cm	2 (9.52%)	2 (18.18%)	4 (30.77%)	3 (60%)	11 (22%)

$X^2 = 7.23$, p = 0.2998 (no significant)
*in 50 penile cancer patients

TABLE 6. **Metastatic node types***

Metastasis	**Sentinel**	**Superficial**	**Deep**	**Pelvic**
	n=18	**n=18**	**n=18**	**n=18**
Positive	16 (88.8)	13 (72.2)	6 (33.3)	4 (22.2)
Negative	2 (11.1)	5 (27.3)	12 (66.7)	14 (77.8)

$X^2 = 21.65$, p =<0.001 (significant)
*Of 50 penile cancer patients, 18 had metastasis and 32 had localized cancer

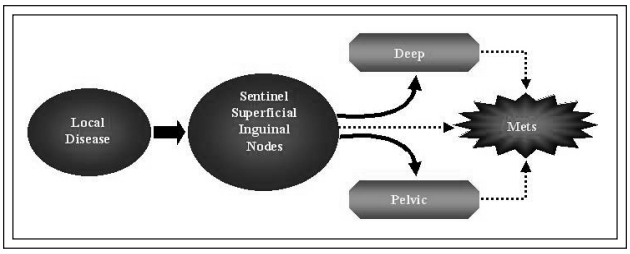

Figure 3. Penile cancer – natural history

Discussion

Most authors agree that local and regional surgery is the treatment of choice in penile cancer.[10,14,15,28,34- 41] The current areas of disagreement are chiefly about optimal management of regional nodes.[2-4,14,28,36,42] Part of this controversy stems from the inability of surgeons to evaluate, in a noninvasive way, the involvement of lymphatic pathways. The inflammatory reaction of the draining regional lymph nodes can cause enlargement without the presence of metastases. On the other hand, 20% of clinically negative nodes have micrometastases.[2-4,14,36,42]

Routine or prophylactic lymphadenectomies performed as a part of oncological surgical treatment are potentially a source of various types of morbidity including seromas, chylous fistula, infections, scar formation, lymphedema, restricted mobility, and cosmetics alterations. For these reasons, it is not advisable to offer lymphadenectomies to all patients with penile cancer.[3,6,11-13,42,43]

When the lymphatic nodes are positive for metastases, in some cases surgery is useful to stage and treat the cancer. Surgical indications, extent of the surgery, preferential lymphatic pathways, and morbidity of lymphadenectomies remains to be determined.[2-4,14,28,36,42] Scientific literature contains reports of many surgical techniques for lymphadenectomies, each with its own advantages of being less invasive or more effective.[3,4,11,28,33,36,40,44-46]

In our prospective study, we tried to correlate the characteristics of the primary lesions and the risk

TABLE 8. **Localized and metastatic disease nodes - follow-up (n = 50)**

	Disease		
Progression	**Localized (I + II) n=32**	**Metastatic (III + IV) n=18**	**Total**
Without	28 (87.5%)	9 (50%)	37 (74%)
With	4 (12.5%)	9 (50%)	13 (26%)

Fisher test; p = 0.0066 (significant)

TABLE 7. **Surgical complications***

Complication type	**Degree/Presence**	**Description**	**Number of cases**
Surgical infection	Level I	Patient treated with antibiotic therapy at home	n = 1 (2%)
	Level II	Patient treated in hospital	n = 5 (10%)
Skin necrosis	Level I	< 25% of surface	n = 3 (6%)
	Level II	25% to 50% of surface	n = 0 (0%)
	Level III	> 50% of surface	n = 0 (0%)
Lymphatic fistula	< 1 week		n = 2 (4%)
	> 1 week		n = 9 (18%)
Lymphocele (drainage)	Yes		n = 2 (4%)
	No		n = 1 (2%)
Inferior limb edema	Level I	Palpable	n = 6 (12%)
	Level II	Visible	n = 3 (6%)
	Level III	Patient finds it difficult to move	n = 0 (0%)
Urethral stenosis (urethrotomy)			n = 3 (6%)
None			n = 25 (50%)
Death			n = 0 (0%)

*in 50 penile cancer patients

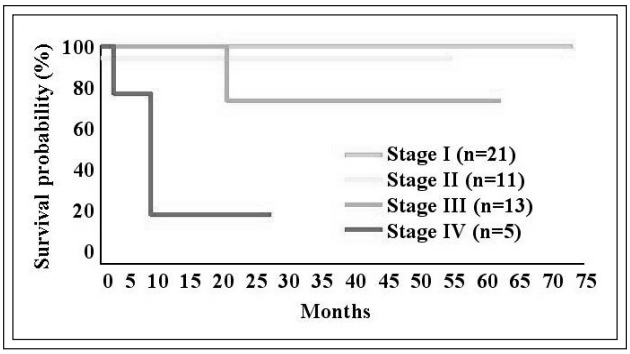

Figure 4. Penile cancer – survival curves (Kaplan-Meier)

factors for cancer dissemination. The way the surgery was routinely performed in stages allowed the histopathological study of the different groups of lymph nodes — that is, sentinel, superficial, deep, and pelvic lymph nodes — and permitted us to compare the results of each isolated dissection. The long follow-up period also allowed us to prove the efficacy of the procedure in selected cases. The morbidity of the operation is significantly less important than in the past, due to better understanding of the vascular system of the skin, more effective drainage, and better control of infections. Based in our findings, we propose the algorithm shown in Figure 5, for patient management after the treatment of the primary lesion.

Conclusions

Risk factors for tumor spread are primary lesions >2 cm in diameter, unfavorable histology findings, and invasive tumors.

The ideal candidates for watchful waiting are patients without the risk factors for tumor spread.

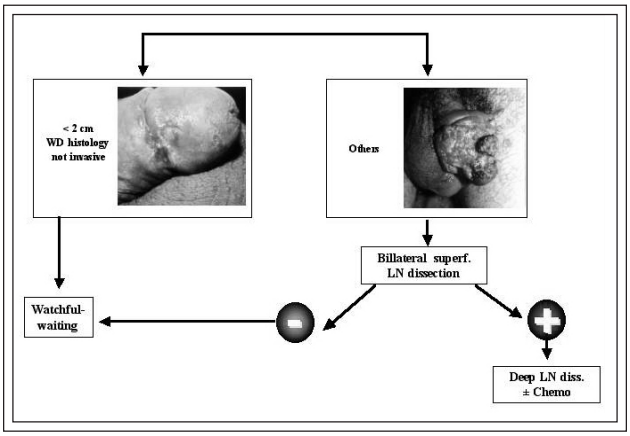

Figure 5. Penile cancer – algorithm for patient management after treatment of the primary lesion

Sentinel nodes were the most commonly infiltrated (88%) lymph nodes, but this did not occur in all positive cases.

When superficial inguinal nodes are negative, it is not necessary to continue the lymphadenectomy of the deep inguinal nodes.

When inguinal nodes are negative, it is not necessary to perform pelvic dissection.

Performing limited surgery on positive nodes risks leaving tumor behind. The superficial bilateral lymphadenectomy is the procedure of choice in cases of clinically negative nodes in patients with risk factors for tumor spread.

Progression of penile cancer is related to the stage and number of positive nodes. There is 10% progression in cases with up to three positive nodes and 42% progression in cases with more than three nodes. □

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