Treatment of the inguinal regions in penile cancer: a review of the literature and treatment proposal

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TAUSSKY D, CROOK J, AL GHAMDI A, FLESHNER N, JEWETT MAS. Treatment of the inguinal regions in penile cancer: a review of the literature and treatment proposal. The Canadian Journal of Urology. 2006;13(1):2978-2983.

Penile cancer is a rare malignancy affecting only 1 per 100,000 men in North America and Western Europe. Although the majority of men present with clinically negative inguinal lymph nodes, node positivity is associated with a very poor prognosis. Both the management of positive nodes, and the management of clinically negative nodes in intermediate- and high-risk patients remain controversial. Experience with penile cancer is often limited as even tertiary referral cancer centers may see only one or two such patients per year. The literature, which consists mainly of retrospective studies of patients treated over several decades, is not conclusive.
We undertook a literature review to address this issue and to propose

Key Words: penile cancer, inguinal lymph nodes

Introduction

Cancer of the penis is a relatively rare cancer, affecting only 1 per 100,000 men in North America and Western Europe. Our literature search revealed an exponential decline in publications on this subject over the last 10 years. There are only two trials in the National Cancer Institute database for penile cancer, and these are investigating chemotherapy regimens in advanced or metastatic disease (SWOG-S0224, EORTC-30992).

Accepted for publication December 2005

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Inguinal lymph node status is predictive for survival[1-7] and the treatment of inguinal lymph nodes is an important aspect of the management of penile cancer both from an oncologic and a morbidity point of view. Lymphadenectomy is effective but is associated with a morbidity rate of 30%-50%[8,9] including infections, deep vein thrombosis, flap necrosis and prolonged edema. The standard teaching for invasive penile cancer, even when inguinal nodes are clinically negative, is bilateral ilio-inguinal lymph node dissection.[10] Only those with superficial cancers and clinically negative nodes may be treated expectantly.

The recently published guidelines of the European Association of Urology (EAU)[8] define three risk groups for patients with non-palpable nodes based

on T-stage and histologic differentiation (low risk: pTis, pTaG1-2 or pT1G1; intermediate risk: pT1G2, and high risk: pT ≥2 or G3. Surveillance is recommended in low risk, and lymphadenectomy in high-risk patients. In the intermediate risk group, the decision is influenced by the presence of vascular or lymphatic invasion and the growth pattern.

In this paper we review the prognostic factors and risk factors for lymph node disease and present a proposal on the management of regional lymph nodes in penile cancer.

Methods

A review of the English literature was undertaken and articles containing pertinent information on the subject were identified.

Lymph node evaluation

Overall prognosis in penile cancer is dependent on nodal stage. However, it is not clear which is the best staging procedure for inguinal lymph nodes. Table 1.

Clinically suspicious nodes are negative on histologic examination in 20%-50% of cases[9,11] while subclinical metastases exist in 18%-66% of patients with clinically normal lymph nodes.[2]

No study has shown an advantage of lymphography, computerized tomography or fine needle aspiration cytology over clinical examination for lymph node evaluation.[12,13] The use of magnetic resonance imaging in the staging of nodal disease has not been studied; however, in the absence of clinical disease, CT and MRI are not recommended for staging.[11] Because of the unreliability of clinical, cytological and radiological staging, more exact staging tools have been sought.

Sentinel lymph node (SLN) evaluation by lymphangiography was initially proposed by Cabanas[14] but this concept has not been validated clinically. Several studies have reported that patients with a negative sentinel node biopsy may later developed positive inguinal nodes.[15] The sentinel node is difficult to locate[16] and the anatomical position can vary.[17] Fine needle aspiration for cytology (FNA) of the SLN can be done under fluoroscopic- or CT-guidance, but the probability of a false negative underlines the difficulty of this procedure and a negative SLN does not preclude treatment of pelvic lymph nodes.[15] Even though negative results do not exclude nodal involvement, observation has been suggested after a negative FNA of the SLN.[18]

Recently, the use of technetium-99 m-labeled colloid has improved identification of the sentinel lymph node. The complication rate is low.[13] It can be used to verify clinically normal lymph nodes[13,17] as well as checking for contralateral disease in cases with unilateral adenopathy.[19] The development of a positive groin after sentinel dissection is uncommon,[13] ranging from as low as 0.25%[20] up to 22%.[19]

Although a trial of antibiotics for clinically positive nodes has been suggested, others favor immediate biopsy.[11] A 6-week interval between treatment of the penile lesion and node-dissection has been suggested to reduce the inflammatory component of adenopathy and to reduce the risk of wound infection.[15]

Surgery, RT or observation?

There is no randomized trial comparing treatment modalities for lymph nodes in penile cancer. Kulkarni et al[21] published a trial on 64 patients with clinically negative nodes (N0, N1-2a) selecting either bilateral inguinal dissection (n=27), RT (n=18) or surveillance (n=19) on a sequential basis. For the various T-stages, survival rates were identical between treatment arms, but N0 patients had a significantly higher survival rate in the surgical group. Nodal relapse occurred in seven patients on surveillance, but only in one after dissection and in two after RT. This study is not supportive of observation of clinically negative groins in general.

Early versus delayed treatment

Retrospective analysis of the outcome of immediate (staging) node dissection versus delayed surgery at the time of the development of adenopathy consistently shows a significantly better 5 year DFS for early LN dissection.[6,22] Furthermore, the incidence of postoperative complications is dependent on the intent of surgery. Prophylactic surgery (cN0) results in fewer complications than therapeutic (cN+) or palliative surgery.[23] This is partially because prophylactic surgery can be limited to a superficial dissection while therapeutic dissection must extend to the deep and possibly pelvic nodes.[23] Lymph node failures in conservatively managed groins may be difficult to salvage and can lead to death.[2,6,21,22,24]

TABLE 1. **Incidence of LN+ in % adapted from Ornellas et al[6]**

	T1 N=56	T2 N=202	T3 N=88	T4 N=14
N0	82	53	31	50
N1	2	14	10	7
N2	14	27	43	29
N3	2	5	16	14

TABLE 2. **Correlation between inguinal and pelvic nodal status adapted from Ravi et al[3]**

No. of positive inguinal LN	Number patients	No. of positive pelvic LN 0		1		2		3		>3	
0	8	8	100%	0	0%	0	0%	0	0%	0	0%
1-3	75	58	77%	4	5%	6	8%	6	8%	1	1%
>3	23	10	44%	5	22%	2	9%	0	0%	4	17%

Pelvic lymph nodes

The presence of positive pelvic lymph nodes is dependent on the number of positive inguinal lymph nodes. With more than three positive inguinal lymph nodes, the chance of positive pelvic lymph nodes is 56%, Table 2. Pelvic lymph nodes are rarely (2.9%) positive in absence of positive inguinal nodes.[3]

Risk factors for LN metastasis

Multivariate analysis has revealed several risk factors for regional spread, Table 3. Tumor stage and differentiation, lymphatic and venous embolization, and vascular invasion are all predictive of regional spread. However, the number of mitosis/HPF, the depth of invasion, tumor thickness and nuclear grade are not predictive. Three risk groups based on tumor stage and differentiation have been identified to predict for lymph node involvement. Low risk patients have T1 G1 tumors, while patients with an intermediate risk of LN involvement have T1 G2-3 or T2-3 G1 cancers. Those cases with T2-3 G2-3 cancers are at high risk.

This stratification correctly identified node negative status in all patients in the low risk group and was correct in 83.3% of the high-risk group. Appropriate treatment for the patients in the intermediate group (33.3% positive lymph nodes) is not yet clear.[25]

Role and extent of groin dissection

Although the classical radical groin dissection is associated with significant acute and chronic complications, modifications have reduced complications to an acceptable level. Understanding the differences between radical and modified dissection, as well as deep and superficial dissection is important.

Radical ilio-inguinal node dissection

The area of dissection is bounded superiorly by a line from anterior iliac spine to the superior margin of the external inguinal ring, laterally by a line inferiorly from the anterior iliac spine for a distance of 20 cm, medially by a line inferiorly from the pubic tubercle for a distance of approximately 15 cm, and inferiorly by a line joining the medial and lateral boundaries. The incision extends from the anterior superior iliac spine toward the pubic tubercle, parallel to the inguinal ligament and is usually about 4 cm to 6 cm long. The encompassed fat and areolar tissues are dissected from the external oblique aponeurosis and the spermatic cord to the inferior border of the inguinal ligament. This maneuver usually begins 4 cm to 5 cm above the level of the inguinal ligament. The inferior angle of the inguino-femoral exposure is at

TABLE 3. **Risk factors on multivariate analysis for pathological involvement of inguinal lymph nodes**

Factor	P=	N=	Reference
Lymphatic embolization	0.0008	145	Lopes et al[28]
Venous embolization	0.041	145	Lopes et al[28]
Stage T1 vs. ≥T2:	0.012	48	Slaton et al[46]
	0.0047	62	Villavicencio et al[43]
	0.001	110	Horenblas et al[39]
Presence of vascular invasion	0.005	48	Slaton et al[46]
Histologic differentiation			
>50% poorly differentiated cancer*	0.0043	48	Slaton et al[46]
Cellular differentiation	0.0041	62	Villavicencio et al[43]
	0.02	42	Theodorescu et al[9]

*In penectomy

the apex of the femoral triangle, where the long saphenous vein is identified. Dissection is deepened through the fascia overlying the sartorius muscle laterally and the adductor muscle medially. At the apex of the femoral triangle, the femoral artery and vein are identified, and dissection is continued superiorly along the femoral vessels.

The saphenous vein is divided at the saphenofemoral junction, and the dissection is continued superiorly until continuity with the pelvic dissection is attained at the femoral canal. After the femoral triangle is dissected, the sartorius muscle is mobilized from its origin at the anterior superior iliac spine and either transposed or rolled medially to cover the femoral vessels.[15]

A radical superficial and deep ilio-inguinal node dissection is indicated for patients with palpable nodes that persist after management of the primary lesion. A 6-week course of antibiotics may be prescribed prior to surgery. If positive nodes are encountered in a limited groin dissection, surgery should be extended. Initially node negative patients who develop clinically palpable nodes later should undergo a unilateral ilio-inguinal node dissection.

0wing to the absence of systemic treatment for metastatic disease, patients with disseminated disease are generally not considered as candidates for groin dissection. However, groin dissection may offer a significant palliative benefit regarding avoidance of devastating complications from advanced regional disease, such as erosion of the femoral vessels.

Modified groin lymphadenectomy

The modified groin dissection or superficial lymphadenectomy differs from standard dissection in that the skin incision is shorter; the node dissection is limited to exclude regions lateral to the femoral artery and caudal to the fossa ovalis. The saphenous veins are preserved and transposition of the sartorius muscle is eliminated.

This dissection is indicated as a staging procedure for clinically negative nodes in high risk patients, or for those with equivocally or minimally enlarged nodes.[26] This procedure is a compromise between the sentinel lymph node biopsy, and the standard extended inguinal lymphadenectomy, which may not be necessary in patients with minimal regional metastases.

Complications

In radical ilio-inguinal node dissection a 30% to 50% incidence of significant morbidity is reported. Although mortality rates in early series were as high as 3.3%,[27] recent series indicate no peri-operative deaths.[3,6,22,28] In the early series, node dissection was performed concomitantly with penectomy, which increased the risk of sepsis. In modified inguinal lymphadenectomy, early complications have been reduced to 6.8% and late complications are only 3.4%.[29]

The most common complications include wound infection, flap necrosis, lymphocele, thrombophlebitis, leg edema and hemorrhage from erosion into the femoral vessels.

Clinical follow-up for observation of groins

A strict follow-up scheme is necessary in expectantly treated patients. The majority of patients treated with radiotherapy have expectant management of the inguinal lymph nodes.[1,24,30,31] Follow-up schedules suggest an assessment every 3 months for the first 2-3 years, every 6 months for year 3-5, and then yearly.[1,11,25,30] Only patients likely to comply with follow-up should be treated conservatively. Time to recurrence in untreated nodes is often short[30,32,33] with a median of about 1.6 years; 75% recur within 2.8 years.[9]

Role of chemotherapy in unresectable nodes

Intravenous chemotherapy regimens employing 5-fluorouracil, mitomycin C[34] and cisplatin or 5-fluorouracil, methotrexate and bleomycin[35] yield limited success. Intra-arterial chemotherapy may be more successful,[36,37] even in advanced disease.

Currently, new agents like Irinotecan IV (EORTC-30992) and docetaxel IV (SWOG-S0224) are being investigated. Concomittant radio-chemotherapy may be promising, although only small non-randomized studies exist.[38]

Role of postoperative radiotherapy

The role of postoperative radiotherapy is not well established. Rozan[31] recommends that in the presence of extensive extra-capsular disease or involvement of more than two nodes[39] at the time of groin dissection, postoperative radiotherapy is indicated to the pelvis and groin, using 50 Gy.[21,24]

In absence of more compelling data, it is reasonable to treat patients with penile cancer in a fashion analogous to vulvar and anal cancers, where more data exist. Vulvar and anal cancer (if situated distal to the dentate line) both have a similar step-wise lymphatic spread from deep inguinal- to pelvic lymph nodes and the frequency of positive lymph nodes depends, as discussed above for penile cancer, on primary tumour size (stage).

In anal cancer, pelvic radiotherapy is recommended when inguinal nodes are positive.[40-43] In vulvar

cancer, the management of inguinal lymph nodes was the subject of a recent Cochrane review.[44] It was concluded that surgery is still the cornerstone of management of the inguinal regions. However, the GOG protocol 37[45] randomized patients to either bilateral inguinal lymphadenectomy or inguinal and pelvic RT for vulvar cancer. Patients receiving RT had a significantly better 2-year survival, which was attributed to the effect of adjuvant pelvic radiotherapy. Patients with clinically involved groin nodes had the biggest survival advantage from pelvic RT. Acute morbidity was less with RT, with shorter hospital stays (only 23% >13 days versus 80%) and less lymphedema (9% versus 16%) but with a higher rate of recurrences (range 4.6%–18.5%).

Conclusion and proposal

In the absence of level 1 evidence from randomized trials, it is difficult to propose an evidence-based guideline. However, the data from retrospective reports, and experience from other tumor-sites with similar lymphatic spread, can be used to propose a reasonable approach to the management of inguinal lymph nodes for penile cancer. The recently published EAU guideline[8] is also helpful in this respect.

Low-risk patients (T1 G1-2) with clinically negative groins can be managed expectantly with regular clinical follow up. A suggested schedule is every 3 months for the first 2 years, then every 6 months for the next 3 years.

Intermediate risk patients (T1G2, T2-3 G1) can be followed expectantly if patients are deemed reliable for follow-up and in the absence of known risk factors such as lympho-vascular invasion. Regular CT examination may be a useful adjunct to clinical examination. If patients seem unlikely to be compliant with regular follow up, a staging superficial LND should be performed. New and promising staging investigations like sentinel LN identification may help to limit the morbidity of LND.

High risk patients (T2-3 or G3) should have bilateral staging superficial LND with consideration of post-operative inguinal and pelvic RT (45-50 Gy) in the case of multiple involved nodes or capsular penetration. □

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