

Exploring the Factors Associated with Inguinal Metastasis in Carcinoma Penis: A Retrospective Analysis

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Abstract

Purpose: We determine if histopathological factors of the primary penile tumor can stratify the risk of the development of inguinal lymph node metastases.

Materials and Methods: Clinical records of 61 consecutive patients with squamous cell carcinoma of the penis who underwent resection of the primary lesion and either inguinal lymph node dissection or were observed for signs of recurrence (median follow-up 36 months) were reviewed.

Parameters examined included pathological tumor stage, quantified depth of invasion and, histological grade, in the primary tumor, and presence or absence of vascular invasion. Variables were compared in 19 lymph node positive and 42 lymph node negative cases.

Results: Pathological tumor stage, vascular invasion and histological grade were the strongest predictors of nodal metastasis on Univariate and multivariate regression analyses. 13 pT1 tumors none of them exhibited vascular invasion and 3 (23%) with lymph node metastases. Of 48 patients with pT2 or greater tumors 12 (25%) had vascular invasion and 16 (33%) had lymph node metastases. No other variables tested were significantly different among the patient cohorts.

Conclusions: Pathological stage of the penile tumor, vascular invasion and histological grade were independent prognostic factors for inguinal lymph node metastasis.

Prophylactic lymphadenectomy in compliant patients with pT1 lesions without vascular invasion and histological grade does not appear warranted.

Keywords: Penile Neoplasms, Lymphatic Metastasis, Neoplasm Staging.

1. INTRODUCTION

The presence and extent of inguinal lymph node metastases are the most significant predictors of survival in men with invasive squamous cell carcinoma of the penis^{1–5}. Physical examination to predict pathologically involved lymph nodes was falsely negative an average of 25% of the time (range 11% to 62%) in a review of 266 cases of penile cancer from 6 different series^{4–9}. Staging strategies, ranging from noninvasive to minimally invasive (including sentinel lymph node sampling techniques), have also been associated with false-negative findings and, thus, the most reliable method of determining the presence of microscopic metastases is inguinal lymphadenectomy^{10, 11}. A number of investigators have reported that early prophylactic inguinal lymphadenectomy in patients with clinically negative lymph nodes results in improved survival compared with delayed lymphadenectomy^{1, 2, 5, 12}. However, inguinal lymphadenectomy is associated with morbidity^{1, 13–15} and, therefore, the selection of patients who are at significant risk for micro-metastases and should undergo “therapeutic” dissection continues to be of paramount importance. Several histopathological factors in the primary penile tumor, such as stage,^{1, 16} growth pattern,¹⁷ grade,^{8, 12, 18–21, 22} depth of invasion^{18–22}, DNA ploidy,²² and presence of vascular or lymphatic invasion,^{12, 19, 23} have been evaluated as predictors of lymph node involvement, and all except DNA ploidy were of prognostic significance. We analyzed a variety of histopathological variables, including tumor stage, vascular invasion, histological grade, depth of invasion within the primary tumors of 61 patients with invasive squamous cell carcinoma of the penis to identify which factors were independently associated with inguinal lymph node metastases.

2. METHODS

We retrospectively reviewed the records of 61 consecutive patients (median age 57 years, range 30–85) with invasive squamous cell carcinoma of the penis who were treated at multiple centres including Kidwai Cancer Institute, Kalyan Singh Super speciality Cancer Institute and Hind Institute of Medical Sciences from 2010 to 2021. Clinical information and pathological material were available for all patients who underwent either resection of the primary lesion and inguinal lymph node dissection or resection of the primary lesion and follow-up with serial physical examinations.

Of the patients 42 were characterized as having localized disease based on either absence of metastases on pathological evaluation of resected lymph nodes (32) or absence of inguinal recurrence on serial physical examinations (10) with a minimum 2-year follow-up. No patient received adjunctive therapy (chemotherapy or prophylactic groin irradiation) before inguinal lymphadenectomy or during observation. The remaining 19 patients exhibited regional lymph node metastases either at presentation (10) or on follow-up examinations a median of 9 months after penectomy (8).

Table 1:- pathological evaluation

Factors	No. of pts	No. of pts with LN mets	Chi-square test	p- value
Stage pT1 pT2 or more	13 48	3 (23 %) 16(33%)	0.2761	0.5992
Vascular invasion No Yes	49 12	9 (18%) 10(83%)	7.893	0.0049
Hist. grade 1 2 or more	26 35	5(19%) 14(40%)	1.623	0.2026
Depth <3mm >3mm	9 52	0(0) 19(36%)	3.159	0.0378

Pathological evaluation. Penectomy specimens were reviewed by the study pathologists to assess the variables listed in table 1. The AJCC 2010, 8 th edition TNM staging system was used to determine the pathological stage of the primary penile tumor 61 Tumors were categorized as pT1 or pT2 or greater. Peritumoral vascular invasion was defined as the presence of tumor emboli within endothelium

lined spaces separated from the primary tumor by at least 1 high power field.

Histological tumor grade was grade 1—well differentiated (no evidence of anaplasia), 2—moderately differentiated (< 50% anaplasia) and 3—poorly differentiated (>50% anaplastic cells), based on a modification of the system proposed by Broders.²⁵

Depth of invasion and tumor thickness were measured in mm based on 2 measurement schemes reported to be prognostic for patients with cervical and vulvar squamous cell cancers, respectively²⁷⁻²⁹. Depth of invasion was measured from the intact basement membrane at the edge of the primary tumor to the deepest tumor cell. Tumor thickness was measured from the top of the tumor to the deepest tumor cell.

Statistical analysis:

We evaluated the relationship between each histopathological factor and the presence of positive lymph nodes. Univariate comparisons were performed using the Student's t test for parameters with continuous values and chi-square analysis for parameters with discontinuous values.³⁰ Cutoff points for continuous variables were arbitrarily chosen based on the best separation of the lymph node positive and negative cohorts using scattergrams of the data points. p : 0.05 was considered statistically significant

3. RESULTS

Prognostic factors for lymph node metastasis:

3 of 13(23%) patient with a pT1 penile cancer exhibited lymph node metastasis compared with 16 of 48 (33%) with pT2 or greater tumors (p= 0.5992, table 1). Nodal metastases were present

in 10 of the 12 patients (83%) with vascular invasion but in only 9 of 49 (83%) without vascular invasion ($p = 0.0049$).

Nodal metastases were present in 5 of the 26 patients (19%) with histological grade 1 and present in 14 of the 35 patients (40%) with histological grade 2 or more ($p = 0.2026$).

Nodal metastases were present in 0 of the 9 patients (0%) with <3 mm depth of lesion and 19 of 52 (36%) present in > 3mm depth of lesion ($p = 0.0378$).

The incidences of nodal metastasis in patients with penile tumors that were T1, T2 or more, histological grade 2 or greater, approached but did not reach statistical significance ($p = 0.599$ and 0.2026 , respectively) compared with tumors that had vascular invasion and depth of invasion more than 3mm.

On analysis only depth of invasion and presence of vascular demonstrated independent prognostic value for lymph node metastasis (table 1).

Table 2

Factors	T1	T2 or more	P value	
no. of patients	13	48		
no. of vascular invasion	0	12		
no. of histological grade 1	8	5		
no. of histological grade 2 or more	18	30		0.12002
depth <3mm	4	5		
depth >3mm	5	43		0.066

Comparison of histopathological factors among pT1 and pT2 or greater penile squamous cancer.

Vascular invasion was absent in all patients with pT1 primary tumors and only 3 out of 13 patient with a pT1 penile tumor exhibited positive lymph nodes. Other significant differences between the stages included a lower incidence of histological grade . grade 1 8 Of 13 (61%) and grade 2 or more in 5 of 13 (38%) in T1 tumours or greater tumors, and lower depths of invasion and tumor thickness in the pT1 cohort

Table 3. Prognostic factors for lymph node metastasis in patients with stage pt2 or greater penile squamous cancer

Factor	No. Pts.	No. With Metastasis (%)	Chi-Square	P value
Vascular invasion:	36	2(5.5)	12.6025	0.000385
No				
Yes	12	9(75)		
Histological grade:	18	5(27.7)	0.085	0.769
1				
2 or more	30	10(33.3)		

Prognostic significance of among pT2 or greater penile squamous cancer.

Because the overall incidence of metastasis was approximately 33% for patients with pT2 or greater tumors, we evaluated whether any of the variables could identify a subset of patients within this cohort with a significantly higher or lower risk for metastasis.

On analysis presence of vascular invasion and depth of invasion of cancer were the only factors that could significantly stratify the risk of metastasis for patients with pT2 or greater tumors ($p = 0.00038$ and 0.08 respectively). Among patients with pT2 or greater tumors lymph nodes were positive in 75% with vascular invasion but in only 5.5% without vascular invasion (table 3).

4. DISCUSSION

To define which factors were independently associated with nodal metastasis, contemporary version of the TNM staging system, 3 different parameters assessing tumor grade (nuclear grade, histological grade and percentage of poorly differentiated cancer) and quantitated measures of invasion previously shown to have prognostic importance in penile, cervical and vulvar cancers.^{19, 22, 27-29} DNA ploidy was omitted from analysis because 2 previous reports revealed that it has no prognostic value for determining the presence of inguinal lymph node metastasis.^{22, 32} Multivariate regression analysis revealed that pathological stage of the penile tumor, vascular invasion and greater than 50% poorly differentiated cancer in the penile tumor specimen were independent predictors of lymph node metastasis.

Primary tumor stage has been a consistently noted prognostic factor for nodal metastasis irrespective of the staging system used.^{1, 5, 6, 10, 12, 20, 21, 24, 33, 34} Involvement of the corpus spongiosum and corpora cavernosa has been associated with a 39% to 67% risk of metastatic disease.^{1, 5, 6, 8, 12, 20, 23}

Our finding that 33% of patients with pT2 or greater tumors had metastatic disease is consistent with these observations. According to the 1997 TNM staging system pT1 penile cancers involve the subepithelial connective tissue only and do not involve the corpus spongiosum, corpora cavernosa or urethra.²⁴ Similarly, staged tumors have been associated with a 23% incidence of nodal metastasis.²⁰⁻²² A recent exception to this relatively low rate of metastatic disease was noted by Theodorescu et al who found that 14 of 24 patients (58%) with pT1 penile tumors and negative nodes on initial clinical assessment had inguinal nodal metastases.⁸ These data suggest that other variables within the penile cancers of their patient cohort may have modified the effect that tumor stage had on metastasis. In our series only 3 of the 13 pT1 tumors metastasized, which is likely due to the absence of vascular invasion (table 2).

Relatively few studies have examined the role of vascular invasion as a prognostic indicator of inguinal lymph node metastasis in penile squamous cancer.^{12, 19, 23} In 1996 Lopes et al reported on the prognostic value of lymphatic invasion in 146 patients with penile cancer.²³ On univariate analysis clinical nodal stage, tumor thickness, lymphatic and venous embolization, and urethral infiltration were associated with the presence of lymph node metastasis. However, on multivariate

analysis only venous and lymphatic invasion remained a significant predictor of positive lymph nodes ($p = 0.04$ and 0.0008 , respectively). Of interest, tumor stage using the 1978 TNM system and histological grade were not predictive of inguinal lymph node metastasis.²³ None of the 13

pT1 tumors in our patient cohort exhibited vascular invasion and of which 3 had lymph node metastasis.

The presence or absence of vascular invasion in patients with pT2 or greater tumors further stratified the risk groups for inguinal lymph node metastasis, as the risk of metastatic disease was 5.5% in patients without and 75 % in those with vascular invasion. Tumor grade has been found to correlate with the likelihood

of metastasis in many studies.^{8, 12, 18, 19, 21} Fraley et al reported an incidence of lymph node metastasis of 5% for grade 1, 79% for grade 2 and 100% for grade 3 tumors.¹² Theodorescu et al noted that the grade of the primary tumor was the only factor predicting nodal relapse and recommended prophylactic lymphadenectomy in patients with grades 2 and 3 primary tumors.⁸ However, 2 more studies using multivariate analysis failed to demonstrate that grade alone was an independent predictor of lymph node involvement.^{21, 22}

In our study there was a trend towards a relationship between histological grade based on the Broders grading system and lymph node metastasis. Failure of this trend to reach significance in our study and others may have been the result of sample size and/or the methodology used to assign a given grade rather than a reflection on how tumor differentiation relates to metastatic potential.

Regarding the latter possibility, our data support the concept that the degree of tumor differentiation is important in predicting metastatic potential but is not evaluated optimally using the Broders system. The 27% incidence of metastasis in the Broders grade 1 tumors (5 patients) in our cohort was significantly lower than the 33% incidence in grade 2 and 3 tumors (10 patients, $p = 0.79$).

Taken together, these data imply that the molecular processes leading to tumor cell invasion into adjacent structures (corpora spongiosum, corpora cavernosa and blood vessels) are the most important predictors of metastasis in addition to histological differentiation. The measured depth of invasion of penile cancer has identified subsets of patients at lower risk for lymph node metastasis.^{22, 23} Hall et al reported that patients with pT1 primary tumors and invasion depth of 5 mm. or less were free of metastasis at up to 10 years of followup.²²

In our study pT1 penile tumors exhibited lower invasion depth and tumor thickness than pT2 or greater tumors ($p=0.066$) which was nearing statistically significant .

5. CONCLUSIONS

Among a large panel of histological variables measured in the same cohort of patients with invasive penile cancer vascular invasion, primary tumor pathological stage (AJCC 2010 version) and provided unique information with which to characterize risk for metastasis. We conclude that “optimal candidates” for a watchful waiting strategy are compliant patients with pT1 penile tumors, no palpable adenopathy, no vascular invasion. Patients with pT2 or greater tumors exhibiting vascular invasion are at significant risk for metastatic disease (75%) and lymphadenectomy is warranted.

The risk of metastatic disease in a small number of patients studied with pT1 tumors and grade 1 with depth < 3mm or selected with pT2 tumors lacking vascular invasion grade 1 may be selected for observation.

However, prospective evaluation of larger patient cohorts exhibiting these features will be necessary to assess the ultimate risk of lymph node metastasis.

FOOT NOTES

Source of Support: Nil

Conflict of Interest: No

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