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ORIGINAL ARTICLE

Male Health

Histological subtype is a significant predictor for inguinal lymph node metastasis in patients with penile squamous cell carcinoma

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The present study aimed to investigate the relationship between histopathological subtype and the probability of inguinal lymph node metastasis (ILNM) in patients with penile squamous cell carcinoma (PSCC). The clinical records of 198 consecutive patients with PSCC were analyzed retrospectively. Primary lesions were reevaluated according to the 2016 World Health Organization (WHO) histopathological classification. We retrieved the clinicopathological factors from the medical records including age, clinical lymph node stage, pathological tumor stage, lymphatic invasion, and nerve invasion. Uni- and multivariate logistic regression analyses were used to explore the risk factors of ILNM. Multivariate analyses identified clinical lymph node stage ($P = 0.000$), pathological tumor stage ($P = 0.016$), histologic grade ($P = 0.000$), and risk group of histological subtypes ($P = 0.029$) as independent predictors for ILNM. Compared with the low-risk group of PSCC subtypes, the intermediate- (HR: 3.66, 95% CI: 1.30–10.37, $P = 0.021$) and high-risk groups (HR: 28.74, 95% CI: 2.37–348.54, $P = 0.008$) were significantly associated with ILNM. In conclusion, the histopathological subtype of the primary lesion is a significant predictor for ILNM in patients with PSCC.

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Keywords: histopathological subtype; inguinal lymph node metastasis; penile neoplasm; squamous cell carcinoma

INTRODUCTION

Penile squamous cell carcinoma (PSCC) is a rare neoplasm.^{1,2} The presence and extent of inguinal lymph node metastases (ILNM) are the most important determinants of survival in patients with PSCC.^{3,4} At present, the selection of patients who are at significant risk for micrometastasis and should undergo “therapeutic” lymphadenectomy continues to be of paramount importance.^{5,6} Multiple clinicopathological factors of the primary penile tumor, such as clinical lymph node stage, tumor grade, histologic grade, growth pattern, and both lymphatic and vascular embolization have been evaluated as significant predictors of ILNM in previous studies.^{3,7,8} The World Health Organization (WHO) classifies PSCC as common, basaloid, verrucous, warty, papillary, sarcomatoid, adenosquamous, mixed, and other rarer histologic subtypes according to their patterns of growth and histological features.⁹

To the best of our knowledge, only few original studies investigated the relationship between histopathological classification and the probability of ILNM in PSCC.^{9–12} Moreover, these studies have several limitations, including the following: the numbers of patients assessed were relatively small owing to the low incidence of PSCC and only univariate analysis was used to explore the risk factors of ILNM in most studies. In addition, there is no unified result to serve as a guideline in clinical practice.

Clinical experience demonstrates a correlation between histological subtypes of squamous cancer and rates of ILNM. The purpose of this article is to investigate whether PSCC subtype is a predictor for ILNM in a large cohort of PSCC patients who were homogeneously diagnosed and treated at the same institution.

PATIENTS AND METHODS

Patient selection and data collection

We retrospectively reviewed the records of 223 consecutive patients with PSCC who were treated at the Second Affiliated Hospital of Anhui Medical University (Hefei, China) from January 2002 to January 2017. Eleven patients who received neoadjuvant therapy or previous groin exploration were excluded, and a total of 14 patients who were subsequently found to be unavailable were excluded because the primary penile lesion was excised elsewhere and pathological review was not possible. Overall, 198 patients were included in the next analysis. Median patient age was 53 (range: 20–84) years.

Information on age and clinical lymph node stage was retrieved from the medical records. The following pathologic variables of the primary tumor were assessed: pathological tumor stage, histopathological grade, lymphatic invasion, nerve invasion, and histological subtype of PSCC. Clinical lymph node stage was assigned by inguinal lymph node palpation and either ultrasound or computed

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tomography scan.¹³ With the exception of age, other factors were coded as categorical variables.

Treatments

Penile tumors were treated surgically. Generally, T1 and T2 tumors smaller than 2 cm were treated with penis-preserving methods while partial amputation was done for larger T2, T3, and T4 tumors. A total of 177 patients underwent bilateral inguinal lymphadenectomy in the prophylactic or therapeutic setting at our center, and a total of 21 patients did not undergo lymphadenectomy because they were evaluated as low risk for ILNM according to the Solsona risk group.¹⁴

Ipsilateral pelvic lymphadenectomy and subsequent adjuvant external radiotherapy have been done when histopathological examination of the inguinal dissected specimen showed extranodal extension, or ≥ 2 inguinal lymph nodes were involved. The borders of ilioinguinal lymphadenectomy were previously described in detail. Surgery was performed by four experienced staff urologists. The radiotherapy dose was usually 50 Gy in 25 fractions and 5 fractions per week.^{15,16} Informed consents were obtained from all patients, and the protocol was approved by the institutional ethics committee of Anhui Medical University, Hefei, China.

Pathological evaluation

Pathologically positive lymph nodes were defined as the presence of histologically confirmed lymph node metastasis in patients who underwent either immediate or delayed inguinal and/or pelvic lymphadenectomy.

Pathological criteria used to classify PSCC subtypes were those described by the 2016 WHO histopathological classification system and the Armed Forces Institute of Pathology.^{9,10} According to these guidelines, PSCC is classified as verrucous, warty, papillary, usual, basaloid, sarcomatoid, adenosquamous, mixed, and other rarer histologic subtypes. To assess the risk of ILNM, the subtypes of PSCC were classified as three groups according to the European Association of Urology (EAU) guideline.¹³ The low-risk group includes verrucous, papillary, and warty types. The intermediate-risk group includes common squamous cell carcinoma (SCC) and mixed forms. High-risk SCC variants are the basaloid, sarcomatoid, adenosquamous, and poorly differentiated types. Penile tumors were staged according to the 2016 American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) system. Histological grade was classified as G1 (well differentiated), G2 (moderately differentiated), and G3–G4 (poorly differentiated) based on the percentage of undifferentiated cells.⁹ Lymphatic invasion was defined as tumor emboli in the vascular lamina of thin walls with or without smooth muscle fibers.⁷

All of the measurements were assessed by two experienced genitourinary pathologists. Any discrepancies were resolved by jointly reviewing the slides.

Follow-up and statistical analysis

Patients were followed up according to a standard protocol. They were seen postoperatively at 2-month intervals during the first 2 years, at 3-month intervals in year 3, and at 6-month intervals thereafter. Follow-up consisted of physical examination with ultrasound and computerized tomography as indicated.

Categorical variables were analyzed using contingency tests (Fisher's exact test, Chi-square test). The continuous data were dichotomized according to the median of each factor. Uni- and multivariate logistic regression analyses were performed to determine the predictors of ILNM. Hazard ratios (HRs) were computed together with 95% confidence intervals (CIs). $P < 0.05$

was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics and univariate analysis of ILNM

Table 1 summarizes clinicopathological characteristics and univariate analysis of variables associated with ILNM in 198 patients. The median age of the group was 53 (range: 20–84) years. After inguinal lymph node dissection, 96 of the 177 patients (54.2%) had ILNM. None of the 21 patients who did not undergo regional lymph node dissection had node metastasis at a follow-up of 2–8 years. These cases were considered node negative. Hence, the ILNM rate of the cohort was 48.5%.

After histopathological classification, we found 122 (61.6%) cases of typical SCC and 76 of SCC variants, including papillary carcinoma in 20 (10.1%), verrucous carcinoma in 10 (5.1%), warty carcinoma in 23 (11.6%), adenosquamous SCC in 2 (1.0%), sarcomatoid SCC in 2 (1.0%), basaloid SCC in 12 (6.1%), and mixed carcinoma in 7 (3.5%), and the ILNM rate of these PSCC subtypes was 58.2%, 5.0%, 10.0%, 26.1%, 100.0%, 100.0%, 75.0%, and 57.1%, respectively ($P = 0.000$).

The lymph node metastatic rate was 15.1%, 54.3%, and 81.3% in low-, intermediate-, and high-risk groups of histological subtypes, respectively ($P = 0.000$). Other variables, such as clinical lymph node stage ($P = 0.000$), tumor stage ($P = 0.000$), histologic grade ($P = 0.000$), and lymphatic invasion ($P = 0.008$) were also prognostic factors on univariate analysis (**Table 1**).

Multivariate analysis of ILNM

The result of multivariate Cox regression analysis for the prediction of ILNM in 198 patients is summarized in **Table 2**. Clinical lymph node stage ($P = 0.000$), tumor stage ($P = 0.016$), histologic grade ($P = 0.000$), and histological subtype of PSCC ($P = 0.029$) were statistically significant predictive factors for ILNM. Compared with the low-risk group of PSCC subtypes, the intermediate- (HR: 3.66, 95% CI: 1.30–10.37, $P = 0.021$) and high-risk groups (HR: 28.74, 95% CI: 2.37–348.54, $P = 0.008$) were significantly associated with ILNM. The HR of 28.74 indicated a more than 28 times relative risk of ILNM due to penile carcinoma in men with high-risk histological subtype group versus men with low-risk group.

DISCUSSION

PSCC spreads mainly through the lymphatic system to inguinal and pelvic lymph nodes.^{3,17} The incidence of LNM is the most important prognostic factor for recurrence, metastasis, and survival in these patients. Criteria for selecting patients who are at significant risk for micrometastases and should undergo inguinal dynamic sentinel lymph node biopsy or lymphadenectomy is still controversial.^{18,19} There are many pathologically based factors that are proved to be important in relation to the rate of ILNM.^{7,20} However, the relationship is still uncertain between histopathological classification and ILNM.

In this article, we retrospectively reviewed the records of 198 consecutive patients with PSCC who were treated at our institution. The results revealed that common SCC predominated but special subtypes together comprised 39.4% of all PSCCs, and the proportion of each group is similar to that of previous literature. Univariate analysis demonstrated that the probability of ILNM is influenced by the histopathological subtype and the risk group of subtypes. Multivariate analyses indicated that the risk group of histopathological subtypes is a significant predictor for ILNM.

Table 1: Clinicopathological characteristics and univariate analysis of variables associated with inguinal lymph node metastases

Variable	Number of patients, n (%)	Number of patients with pN+, n (%)	P
Age (year)			
≤53	100 (50.5)	49 (49.0)	0.884
>53	98 (49.5)	47 (48.0)	
Clinical LN stage			
cN0	126 (63.6)	35 (27.8)	0.000
cN1–3	72 (36.4)	61 (84.7)	
pT stage			
Ta–T1	53 (26.8)	6 (11.3)	0.000
T2	130 (65.7)	79 (60.8)	
T3–T4	15 (7.6)	11 (73.3)	
Histologic grade			
G1	97 (49.0)	19 (19.6)	0.000
G2	72 (36.4)	53 (73.6)	
G3–G4	29 (14.6)	24 (82.8)	
Lymphatic invasion			
No	186 (93.9)	86 (46.2)	0.008
Yes	12 (6.1)	10 (83.3)	
Nerve invasion			
No	191 (96.5)	92 (48.2)	0.935
Yes	7 (3.5)	4 (57.1)	
Histological subtypes			
Papillary carcinoma	20 (10.1)	1 (5.0)	0.000
Verrucous carcinoma	10 (5.1)	1 (10.0)	
Warty carcinoma	23 (11.6)	6 (26.1)	
Common SCC	122 (61.6)	71 (58.2)	
Mixed carcinoma	7 (3.5)	4 (57.1)	
Adenosquamous carcinoma	2 (1.0)	2 (100.0)	
Sarcomatoid carcinoma	2 (1.0)	2 (100.0)	
Basaloid carcinoma	12 (6.1)	9 (75.0)	
Risk group of histological subtypes			
Low risk	53 (26.8)	8 (15.1)	
Intermediate risk	129 (65.2)	70 (54.3)	
High risk	16 (8.1)	13 (81.3)	

LN: lymph node; pN+: pathological lymph node stage; pT: pathological tumor; SCC: squamous cell carcinoma; N0: no palpable or visibly enlarged inguinal lymph nodes; N1: palpable mobile unilateral inguinal lymph node; N2: palpable mobile multiple or bilateral inguinal lymph nodes; N3: fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral; pT stage: penile tumors were staged according to the 2016 AJCC TNM system. Histological grade was classified as G1, G2, and G3–G4 based on the percentage of undifferentiated cells. AJCC: American Joint Committee on Cancer; TNM: tumor, node, metastasis; G1: well differentiated; G2: moderately differentiated; G3–G4: poorly differentiated

Table 2: Multivariate analysis of variables associated with inguinal lymph node metastases

Variable	HR (95% CI)	P
Clinical LN stage (cN1–3 vs cN0)	8.58 (3.37–21.87)	0.000
pT stage		0.016
T2 versus Ta–T1	6.37 (1.67–24.35)	0.007
T3–T4 versus Ta–T1	10.98 (1.59–75.64)	0.015
Histologic grade		0.000
G2 versus G1	7.62 (3.106–18.74)	0.000
G3–G4 versus G1	9.13 (2.00–41.57)	0.004
Lymphovascular (yes vs no)	2.84 (0.40–20.01)	0.296
Histological subtypes		0.029
Intermediate risk versus low risk	3.66 (1.30–10.37)	0.021
High risk versus low risk	28.74 (2.37–348.54)	0.008

CI: confidence interval; pT: pathological tumor; HR: hazard ratio; N0: No palpable or visibly enlarged inguinal lymph nodes; N1: palpable mobile unilateral inguinal lymph node; N2: palpable mobile multiple or bilateral inguinal lymph nodes; N3: fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral; pT stage: penile tumors were staged according to the 2016 AJCC TNM system. Histological grade was classified as G1, G2, and G3–G4 based on the percentage of undifferentiated cells. AJCC: American Joint Committee on Cancer; TNM: tumor, node, metastasis; G1: well differentiated; G2: moderately differentiated; G3–G4: poorly differentiated

Few relative studies tried to examine the role of histopathological subtypes as a prognostic indicator of ILNM in penile squamous cancer. In 2001, Cubilla *et al.*¹² retrospectively reviewed the clinical and pathologic features of 61 cases of PSCC. They found a high rate of nodal metastasis for the basaloid and sarcomatoid neoplasms, only one patient with a verruciform tumor had inguinal node metastasis, and an intermediate rate of metastasis (54%) was found for typical SCC.¹² A second study retrospectively reviewed the records of 72 Chinese patients with PSCC, and no patients with verrucous carcinoma had ILNM. However, 100% of patients with basaloid, 30% with typical, and 33.3% with warty carcinoma had ILNM, and the authors found that histopathological classification was a significant predictor of ILNM in patients with PSCC ($P = 0.002$).¹¹ The last study evaluated clinicopathological features and outcomes in 333 patients with PSCC in Brazil, after comparing the ILNM rates between different PSCC histological subtypes, they found three nodal metastasis risk groups, including low-risk (verrucous, papillary, and warty), intermediate-risk (usual and mixed), and high-risk (sarcomatoid, basaloid, and adenosquamous) groups.¹⁰ This conclusion is adopted by the EAU guidelines.¹³

However, only univariate analysis was used to explore the predictive value of histopathological subtype for ILNM in these studies, and they did not indicate whether patients who received neoadjuvant therapy were excluded. In this study, all the 198 cases without neoadjuvant therapy or previous groin exploration were treated at our institution by four experienced staff urologists. The histopathological subtypes were assessed by two experienced genitourinary pathologists; discrepancies were resolved by a joint review of the slides. Both uni- and multivariate analyses showed that histopathological subtype is an independent predictor for ILNM. We believe that this result is more reliable than previous conclusions.

How to explain this phenomenon? Data analysis showed that the higher the risk group is, the worse the clinical LN stage, pathologic tumor stage, and histologic grade the patients have. That means different SCC subtypes have different biological behaviors and microscopic characteristics. According to the 2016 WHO histopathological classification system, PSCC can be classified as usual, verrucous, papillary, warty, basaloid, sarcomatoid, adenosquamous, mixed, and other rarer histologic subtypes.⁹

The common type of SCC accounts for 48%–65% of penile carcinoma according to the literature, and the 61.6% ratio in our study was similar.²¹ Remarkably, an irregular ulcerated exophytic or endophytic mass partially or totally replacing the glans was typical. Microscopically, the tumors vary from well-differentiated keratinizing tumors to solid anaplastic carcinomas with scant keratinization. Most tumors are of moderate differentiation with high keratinization. Poorly differentiated carcinomas show focally unusual histologic features such as solid, trabecular, sarcomatoid, or clear cell.^{20,21} In our study, the incidence rate of ILNM was 58.2% and this was higher than 30%–40% in previous studies.²¹ One of the reasons leading to this result may be delayed treatment. Most patients delayed their treatment because of poor economic conditions or psychological reasons, and 73.2% of patients' pathologic tumor stage of the whole cohort was higher than T1.

Verruciform tumors, including verrucous, warty, and papillary carcinoma, are exophytic, papillomatous, low-grade lesions. Each subtype has distinctive morphological features that allow a correct classification in most cases.⁹ Verrucous carcinoma represents 3%–8% of penile carcinomas. It is a well-differentiated papillary neoplasm with acanthosis and hyperkeratosis. Verrucous carcinoma is consistently HPV negative. Remarkably, it exhibits a cobblestone to filiform appearance and spiky surface. Microscopically, there are extreme squamous differentiation, papillomatosis, acanthosis, and a broadly based interface between the tumor and stroma. In our cohort, the rate of verrucous carcinoma was 5.1% and one of ten patients developed ILNM. In general, verrucous carcinoma is not associated with ILNM and the mortality rate is 0%.^{13,20,21}

Papillary carcinoma is another verruciform tumor and accounts for 5%–12% of PSCC. The gross findings of papillary carcinoma are exophytic, large, and irregular masses. Microscopically, the appearance is that of a low-grade papillary squamous neoplasm. There are hyperkeratosis and papillomatosis. ILNM occurred in only one of twenty patients in the cohort. The recurrence rate is low, the rate of ILNM is <12%, and the mortality rate is low (0–6%).^{11,20}

Warty carcinoma is a HPV-related condylomatous tumor and accounts for 7%–10% of penile carcinomas. The most conspicuous microscopic features are prominent nuclear atypia of a koilocytotic type and clear cytoplasm. A moderate differentiation and invasion of the corpus spongiosum is the typical presentation, with a low but definite risk for nodal metastasis. The ILNM rate is 26.1% in this study, and about 17%–25% in literature.^{13,20,21}

Basaloid carcinoma is an aggressive HPV-related tumor, representing 9%–14% of all PSCCs. An ulcerated nonexophytic irregular mass is present generally. Microscopically, solid nests of small uniform basaloid cells are found, usually with central necrosis or central abrupt keratinization. The tumor cells tend to deeply infiltrate into the adjacent tissues. The ILNM rate is about 50%–100%, and up to one-third of patients will die of systemic metastases.²⁰

Sarcomatoid carcinoma accounts for 1%–3% of PSCC; it is developed by metaplastic spindle cell transformation of usual SCC and has a poor prognosis. Almost all sarcomatoid carcinomas arise in the surface epithelium of glans but rarely in the foreskin; they are bulky, ulcerated, or rounded polypoid masses grossly. Microscopically, variable proportions of squamous cell and spindle cell carcinomas are present, and the latter predominates. Most patients have ILNM at the time of diagnosis and many have distant dissemination by that time. Mortality is high (50%–90%).¹¹

Adenosquamous carcinoma is thought to arise from the epithelial surface of the glans, it is a rare tumor. Grossly, a granular, large neoplasm invading the penile corpora deeply is present. Microscopically, a mixed squamous cell mucin-producing adenocarcinoma pattern is seen. It is a locoregionally aggressive tumor, the ILNM rate is more than 50%.¹³

Mixed tumors are another category in which interobserver variability may be significant. The typical presentation is similar to that of the usual SCC, with a well-to-poorly differentiated carcinoma invading up to the corpus spongiosum. Microscopically, variable proportions of squamous, warty, and sarcomatoid carcinomas are present. The prognosis is poor, and the rate of ILNM is higher than that in warty, but lower than that in basaloid SCC.^{9,20}

Our study showed that the intermediate- (HR: 3.66, 95% CI: 1.30–10.37, $P = 0.021$) and high-risk groups (HR: 28.74, 95% CI: 2.37–348.54, $P = 0.008$) of PSCC subtypes are significantly associated with ILNM, compared with the low-risk group. However, it must be pointed out that the WHO histopathological classification system has not been widely applied to clinical practice. It is not hard for a pathologist to access the subtypes of PSCC. Moreover, there are some advantages for judging tumor histopathological classification, including (1) etiologically identifying morphological patterns associated with special causative factors and (2) biologically identifying subtypes of tumors with a distinctive morphology related to a good or adverse prognosis. Understanding the histopathological classification of PSCC may help urologists communicate better with patients and prepare a prophylactic systemic treatment in order to improve the outcome and quality of life. Meanwhile, the patient's family can also carry out the psychological preparation of all aspects.

Other factors such as clinical lymph node stage, tumor stage, and histologic grade were shown to be associated with ILNM, but lymphatic invasion failed to be confirmed as an independent risk factor in multivariate analysis. One of the reasons leading to this result may be the relatively low prevalence of lymphatic invasion, there were just 12 cases diagnosed with lymphatic invasion in all the cohorts. In addition, we found that the pathologic tumor stage is mostly T2 or T3 for patients with vascular invasion, and most of them had enlarged groin lymph nodes.

The present study did have certain limitations. (1) The study population was retrospectively enrolled from a single center in China. Although this is one of the largest series, the characteristics of our patients may be different from those of their counterparts at other centers. (2) We did not explore the relationship between histological subtypes and ILNM in patients with clinical negative lymph node, because most of these patients are of low- and intermediate-risk

histological subtypes, only nine patients are of high-risk histological subtypes. (3) Another limitation may be that surgery was not performed by one urologist. Nevertheless, our study is one of the largest series to date on histopathological classification of PSCC and identifies histological subtype as a significant predictor for ILNM.

CONCLUSIONS

Multivariate analysis revealed that the histopathological subtype of the primary lesion is a significant predictor for ILNM in patients with PSCC. The low-risk group is recommended for follow-up observation, and the high-risk group is recommended for inguinal lymphadenectomy, while the intermediate-risk group requires a combination of other predictors to work out a plan.

AUTHOR CONTRIBUTIONS

JYW and MZG designed the study, collected, analyzed, and interpreted the clinical data, wrote the manuscript and revised the manuscript. DDX and YW reviewed pathological slides and revised the manuscript. DXY conceived of the study, participated in its design and coordination, worked as the principal surgeon, supervised the project, and revised the manuscript. LKB, TZ, and DMD collected partial patients' clinical data and followed up the patients. All authors vouch for the respective data and analysis, approved the final version, and agreed to publish the manuscript.

COMPETING FINANCIAL INTERESTS

All authors declare no competing interests.

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