Review Article: Oncology: Genitourinary Cancer

Penile cancer: prognostic factors for lymph node involvement—a narrative review

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Background and Objective: Penile cancer is a kind of urogenital system tumour that seriously affects patients. The status of lymph node metastasis (LNM) is closely related to the treatment and survival of patients. Accurately predicting LNM has been the focus of many clinicians. In this review, we hoped that it can help to systematically understand the influencing factors of LNM in clinical practice.

Methods: In our study, the English-language articles were searched in PubMed during 31 years (1992/01/01–2022/10/01). We searched the MeSH term in [Title/Abstract]: penile neoplasm, penile cancer, penile tumor, penile squamous cell carcinoma, prognosis, prognostic factors, lymphatic metastases, lymph node metastasis.

Key Content and Findings: Several factors are associated with the metastasis of penile squamous cell carcinoma (PSCC) to inguinal lymph nodes. There are still many choices that the current guidelines recommend predictors of LNM. From initial single clinical pathological factors, haematological indices, immunohistochemical indices, and molecular indices to multifactor joint prediction models, there is still no unified gold standard after the review of a large number of studies.

Conclusions: A multitude of markers of LNM for penile cancer. Clinicopathological factors are still important factors for predicting LNM and also important components of prediction models. The molecular indicators will be potential molecular indicators.

Keywords: Penile neoplasms; lymphatic metastasis; predictor

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Introduction

In industrialized countries, penile cancer is uncommon (1,2); however, in some other parts of the world, the incidence can account for 1–2% of malignant diseases in men (3). Penile squamous cell carcinoma (PSCC) is the most common pathological type, and lymph node metastasis (LNM) is the earliest and most common site of metastasis in PSCC (3,4). Because of the limitations in developing countries, LNM has already occurred when the disease is diagnosed (5,6). The 5-year survival rate of patients without LNM is higher than 90% and patients with LNM is about 50% (5). The management of lymph nodes with appropriate staging directly affects the prognosis and survival of patients (7,8). Therefore, the timely and accurate prediction of patients' LNM status can significantly reduce overtreatment, and promote active treatment to improve patient survival

Table 1 The search strategy summary

Items	Specification
Date of search	2022/09/12–2022/10/01
Databases and other sources searched	PubMed
Search terms used	penile cancer, penile tumor, penile neoplasm, penile squamous cell carcinoma, prognostic factors, prognosis, lymphatic metastases, lymph node metastasis, lymph node metastases
Timeframe	1992/01/01–2022/10/01
Inclusion and exclusion criteria	Inclusion criteria: research articles and reviews in English about themes such as penile cancer and lymphatic metastases. Exclusion criteria: some papers which we considered with low reliability
Selection process	Zaishang Li conducted the selection, all authors attended a meeting to discuss the literature selection and obtained the consensus

(9-11). However, different prediction factors have different prediction values. From initial single clinical pathological factors, haematological indices, immunohistochemical indices, and molecular indices to multifactor joint prediction models, there is still no consensus on the criteria for predicting LNM. This article discusses the current approaches in establishing prognostic factors for the lymph node involvement of PSCC, especially inguinal LNM, summarizes the ongoing research results and describes the future research direction in this field of the disease. This review is better than others that systematic analysis of influencing factors from image to molecular mechanism with extensive literatures (12-14). The purpose of this study is to summarize the markers of LNM for penile cancer patients and their therapeutic significance, limitations and future prospects. It is hoped that it can help to systematically understand the influencing factors of LNM in clinical practice. We present this article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-22-59/rc).

Methods

We identified the last 31 years (1992–2022) published studies in PubMed. We searched the MeSH term in [Title/Abstract]: penile neoplasm, penile cancer, penile tumor, penile squamous cell carcinoma, prognosis, prognostic factors, lymphatic metastases, lymph node metastasis. *Table 1* has more details of the method.

Imaging factors

For patients with no palpable lymph nodes, the proportion of micrometastatic disease is approximately 25%, which is hard to diagnose with computed tomography or magnetic resonance imaging (15,16). Twelve studies were included in a meta-analysis, which revealed similar diagnostic accuracies for the detection of inguinal and pelvic LNMs in PSCC patients (17). The standardized uptake value (SUV) (i.e., increased [18F]FDG uptake), is closely related to the differentiation between (post) inflammatory and LNM (18). There was no significant difference in the SUVmean and SUVmax between true positive and false LNM (19). Despite the increased accuracy of positron emission tomography computed tomography (PET-CT), there is still no unified standard for predicting LNM (20,21).

The longitudinal/transverse diameter (L/T) ratio and the presence or absence of an echogenic hilum were also highly specific for malignancy using inguinal ultrasound (7.5 MHz) (22). Although the results of this work are encouraging, such indicators are still used for clinical auxiliary diagnosis or to recommend sentinel lymph node biopsy for staging (23,24). Imaging is used for preoperative evaluation of the size, extent and structures, but it is not recommended to predict the risk of LNM alone.

Clinical factors

Palpable lymph node enlargement highly suggests LNM (3,4,25). The guidelines recommend that palpably groin lymph nodes should be removed, and pathologically assessed. Even enlarged fixed inguinal lymph nodes are more likely to be associated with a high risk of progression, which requires multimodal treatment (3,4,26,27).

Multicentre data confirmed that clinical staging was positively correlated with inguinal LNM (25,28,29).

According to the Northeast Uro-Oncological Group data, the rates of inguinal LNM in cT1, cT2 and cT3–4 patients are 25%, 34% and 66%, respectively (25). An analysis of the SEER database showed that 41.5% of patients with tumour invading the corpus spongiosum and 36.4% of patients with tumour invading the corpus cavernosum have signs of tumour metastasis, which is significantly higher than that in T1 patients (30). In 2017, the new American Joint Committee on Cancer-TNM staging system was adopted (31). Similar to previous results, the study by Kearns *et al.* showed no increased risk of LNM between T2 and T3 disease (32).

The incidence of PSCC increases with age, and the highest incidence is in the sixth decade (2,33). Whether the age of patients at the time of diagnosis can predict LNM remains controversial. The probability of LNM in patients aged <50 years is 39–58%, which is similar to that in patients aged >50 years (48–54%) (28,29,34). Recent research data show that age is an independent risk factor for predicting LNM (diagnosis age >70 years, risk ratio 0.199, 95% CI: 0.066–0.602) (35).

The prognosis of cancer patients were also is influenced by Body mass index (BMI). The association between BMI and cancer survival in penile cancer were confirmed in studies (36-39). However, the association between BMI and LNM was not statistically significant (36). The predictive value of BMI still needs to be further clarified.

Pathological factors

Many pathological features of the primary lesion have been confirmed to be closely related to inguinal LNM (3,4). Different histological types of penile cancer have different metastatic risk rates (30,40). Inguinal LNM is rare in penile sebaceous cell carcinoma, but it can very easy to occur in penile basal cell squamous cell carcinoma. The rate of inguinal LNM in typical PSCC is somewhere in between (41,42).

Human papilloma virus (HPV) infection is a risk factor for PSCC and the most common HPV subtypes are types 16 and 18 (40,43-45). As early as 2001, Bezerra *et al.* found that 73.2% of HPV-negative and 26.2% of HPV-positive patients with primary tumour had LNM (46). With further study of the molecular mechanism, the difference in LNM for HPV-positive *vs.* HPV-negative cases was subsequently confirmed by numerous studies (47-49). A modified Node stage incorporating high risk HPV status can improved the prognostic stratification in LNM patients (50).

There is a significant correlation between the local invasion scope of the primary tumour and the risk of regional LNM (51,52). National Cancer Database was used to evaluate the prognostic ability of the 8th edition of the AJCC TNM staging system. Although this study found that the new TNM staging system not improve the current staging guidelines, the risk rates of inguinal LNM in T2 as spongiosal invasion and T3 as cavernosal invasion were 34% and 45%, respectively. In univariable and multivariable analyses, T classification was significantly associated with node-positive disease (32). A meta-analysis showed that patients with corpora cavernosa invasion had a higher rate of metastasis than those with corpora spongiosa invasion according to the eighth edition tumour stage (53).

The histological grade of the tumour has been proven to be an important index for predicting regional LNM (30,32,54-56). The LNM had a statistically significant relationship with tumour grade (P<0.001) (56). Multivariate analysis showed that a higher grade was a high risk factor for LNM in PSCC patients (30).

Lymphovascular/venous invasion was confirmed to be an important prognostic factor of lymph node status (13,25,57,58). A National Cancer Database analysis showed that lymphovascular invasion (LVI) was the strongest independent predictor of LNM (57). A similar suggestion has been made by other authors (14). In addition to the above factors, clinical research also confirmed that tumour perineural invasion, tumour size, grade and depth of invasion the primary tumour are predictors of LNM (*Table 2*).

Hematological factors

Haematologic abnormalities have been considered prognostic factors for lymph node involvement. SCC-Ag is a tumour-associated protein that has been proven to be closely related to LNM in PSCC (68-70). A meta-analysis revealed that SCC-Ag is a predictor of LNM (OR =8.52, 95% CI: 4.09–17.78; P<0.001) (71). In 2021, Wu *et al.* showed that SCC-Ag can even indicate extranodal invasion (72). However, the threshold range of SCC-Ag is 1.4–2.0 ng/mL, and there is still no consensus on how to determine the threshold value (68-70).

Inflammation plays an important role in the LNM of penile cancer (73,74). Immune-related biomarkers as predictors of LNM were reported in studies. C-reactive protein (CRP) is an indicator of acute and chronic inflammation in penile cancer (70,75). The CRP level was significantly correlated with nodal disease: 53.3% of all patients with CRP >15 and 16.3% of those with CRP

Table 2 Pathological factors in penile cancer

Predictor	Lymph node metastasis	
	Presence	Absence
Perineural invasion (58-60)	30–69%	6–33%
Depth of invasion (5 mm) (61-63)	16–48%	6–17%
Tumour size (3 cm) (30,62,64,65)	35–77%	12–46%
Koilocytosis (61,66,67)	23–79%	45–82%
Angiolymphatic invasion (66)	88%	41%

≤15 mg/L had penile cancer (76). The level of systematic inflammation was also reflected by an economical biomarker—neutrophil-to-lymphocyte ratio (NLR). Recent studies have shown that NLR is directly associated with the prediction of inguinal LNM (77,78). In addition, a meta-analysis indicated that NLR could weaken the persuasiveness of these conclusions (71).

Chemokine (C-X-C motif) ligands (CXCLs) are important regulators of tumour progression in many cancers. Recent studies confirmed that CXCL5 (79) and CXCL13 (80) are potential cancer biomarkers for LNM in penile cancer. However, these indicators need to be further studied to determine their clinical value.

Immunohistochemistry factors

The tumour suppressor gene P53 is involved in tumour progression. In 2002, Lopes *et al.* first evaluated the prognostic value of P53 in PSCC. They found that the proportions of patients with P53-negative and P53-positive inguinal LNM were 39.6% and 67.6% (P=0.01), respectively. P53 was an independent predictor of inguinal LNM (HR 4.8, 95% CI: 1.6–14.9) (28). The value of P53 in predicting LNM was subsequently confirmed by many studies (28). The value of P53 in predicting LNM was subsequently confirmed by many studies (81-83).

Ki-67 is a nuclear matrix protein different from histones. The measurement of its expression level by immunostaining is a reliable method to evaluate the proliferation of tumour cells (84). In 2005, Berdjis *et al.* first evaluated the predictive value of Ki-67 in penile cancer and did not find that Ki-67 was statistically significant in predicting LNM (P=0.07) (85). Guimarães *et al.* found that MIB-1/Ki-67 (>10%) was positively correlated with inguinal LNM (86). Zhu *et al.* reached the same conclusion (81). However, Stankiewicz *et al.* found that Ki-67 protein was strongly positively correlated with tumour grade (P<0.0001) but not with stage (P=0.2193) or lymph node status (P=0.7366) (87).

Cancer immunotherapy can be directed with programmed death ligand 1 (PD-L1) (88). Previous studies have shown that up to 50% of penile cancers express PD-L1, which is positively correlated with LNM in penile cancer (89-91). The incidence of LNM in the PD-L1-positive group was 52% in Hu *et al.*'s study (91), which was different with Davidsson *et al.* (47.7%) (92), Udager *et al.* (47.6%) (89) and Deng *et al.* (43.5%) (90).

There is divergence in association between penile cancer and HPV with different subtypes of PSCC (3,4). Immunohistochemical staining can detect the overexpression of p16INK4a, which can be used as a marker of transcriptionally active HPV infection (93). Tang *et al.* reported that 49.5% (59 of 119) of penile carcinoma patients with samples subjected to immunohistochemistry staining were p16INK4a positive, with no association between p16INK4a status and lymph node status (94). The International Society of Urological Pathology recommends the use of p16INK4A immunostaining for the diagnosis and classification of HPV-related penile cancer (84). HPV infection participates in tumour progression by overexpressing the E7 and E6 oncoproteins and binding and inhibiting the P53 and Rb gene products (41,93,95). Study reported that P53 positivity was a predictor of LNM in p16INK4a negative patients (82). Therefore, overexpression of p16INK4a can be used as one of the markers of virus accumulation; however, whether it can be used as a predictor of LNM still needs to be further determined.

Other biomarkers have been studied in penile malignancies (*Table 3*).

MicroRNAs

In recent years, the use of microRNAs as biomarkers

Table 3 Biomarkers in penile cancer

Predictor	Positive with ILNM/ total patients (%)	Negative with ILNM/ total patients (%)	Nature and function
E-cadherin (29,81)	31/81 (38.3%); 11/51 (21.6%)	22/37 (59.5%); 19/42 (45.2%)	A member of the cadherin family that connects the cytoskeleton with the extracellular environment in epithelial cells and participates in cell signal transduction
MMP-2 (29)	37/90 (41.1%)	16/28 (57.1%)	A zinc-dependent enzyme that cleaves extracellular matrix components. It belongs to the MMP family and plays an important role in regulating stem cell migration and tumour metastasis
MMP-9 (29,81)	18/32 (56.3%); 17/51 (33.3%)	35/88 (39.8%); 13/52 (25.0%)	A zinc-dependent enzyme that can cut extracellular matrix components. It belongs to the MMP family and participates in the degradation of extracellular matrix in normal physiological processes (such as embryonic development, reproduction, angiogenesis, bone development, wound healing, cell migration, learning and memory) and pathological processes
CEACAM19 (96)	18/30 (60.0%)	6/34 (17.6%)	It is a member of carcinoembryonic antigen family and belongs to immunoglobulin superfamily adhesion molecules. It plays an important role in regulating epithelial cell proliferation, apoptosis, lymphocyte activation, angiogenesis, cell migration and other biological processes
HOXD11 (97)	63/85 (74.1%)	64/182 (35.2%)	It belongs to HOX, a superfamily of regulatory genes, and is involved in tumour cell susceptibility to chemotherapy, promotion of apoptosis, and downregulation of invasiveness
LAMC2 (98)	31/56 (55.4%)	16/58 (27.6%)	A multi-adherent extracellular matrix protein that plays an important role in the differentiation, migration and proliferation of tumour cells. It may also be a potential tumour marker
SOD2 (63)	28/53 (52.8%)	15/65 (23.1%)	An antioxidant gene that is a member of the SOD family and has an antitumour effect. Its high expression can enhance the ability of tumour cells to eliminate reactive oxygen species and inhibit tumour growth and the malignant phenotype

LNM, inguinal lymph node metastasis; MMP, matrix metalloproteinase; HOX, Hox genes; SOD, superoxide dismutase.

has attracted attention not only in understanding the pathophysiology of potential diseases but also in the diagnosis and screening of different cancers. In 2020, an analysis of data from Brazil demonstrated that higher expression of miR-223-3p, miR-107, and miR-21-5p was correlated with poor prognosis, and upregulation of miR-223-3p was associated with LNM in PSCC (99). Ayoubian *et al.* reported that the downregulation of miR-137 and miR-328-3p was more characteristic of patients with metastatic disease (100). Tan *et al.* indicated that miR-138-5p functioned as a tumour suppressor in PSCC by inhibiting the translation of HOXD11 post-transcriptionally by binding to the 3' untranslated region, and it was associated with lymph node stage (97).

Multiple factors

The use of a single marker may not be optimal, and numerous studies have attempted to use multiple factors or models containing multiple factors to attempt to identify specific targets for LNM. Solsona *et al.* proposed a stratification that included the stage and grade (101,102). Similarly, the EAU guidelines recommended a risk group using the same pathologic features that have been validated in series (103,104). Other studies also developed some simple prediction models (54,56,57,65). Using the same theoretical approach, some nomograms were proposed to predict the probability of LNM (30,35,72,91,105-112) (*Table 4*).

Conclusions

The mode and clinical significance of LNM of penile cancer have been determined. The prediction of inguinal LNM before surgery has remained a focus of research. Accurate prediction of LNM can avoid overtreatment and missed diagnosis. Due to the lack of randomized clinical

Table 4 Risk group stratification in penile cancer

Study	Number	Content	Evaluation indicator	Type
Solsona *et al.* (101-103)	101	Low risk: stage T1G1 tumours; intermediate risk: stage T2–T3G1 tumours; high risk: stage T2–T3G2–3 tumours	AUC: 0.697 (95% CI: 0.618–0.777)	RGS
EAU risk group (103,104)	175	Low risk: stage pTis, pTaG1-2, and pT1G1 tumours; intermediate risk: stage pT1G2 tumours; high risk: stage pT2 or higher or G3 tumours	AUC: 0.632 (95% CI: 0.548–0.715)	RGS
Sali *et al.* (54)	142	pT2 tumours invaded CS/CC without LVI or PNI and were not grade 3, whereas pT3 tumours invaded CS/CC, showed LVI and/or PNI, or were grade 3	–	RGS
Sali *et al.* (56)	162	Three risk groups were created based on the following: G [1–3]; anatomical level of infiltration [1–3]; and tumour infiltration pattern [1–3]	AUC: 0.72	RGS
Patel *et al.* (65)	102	Clinico-radio-pathological Risk Scoring System: size of the primary >3 cm, ulceroinfiltrative growth, involving shaft, ultrasound size of lymph nodes >1 cm, loss of fatty hila, moderate and poor differentiation, LVI and/or PNI	AUC: 0.91	RGS
Zhang *et al.* (30)	1,016	Age, primary tumour site, G, tumour size, and T stage	C-index: 0.776; AUC: 0.776 (95% CI: 0.739–0.812)	Nomogram
Ficarra *et al.* (105)	175	Clinical stage of inguinal lymph nodes, tumour thickness, growth pattern, histological grade, presence of LVI, CC infiltration, CS infiltration and urethral infiltration	AUC: 0.867	Nomogram
Shao *et al.* (35)	300 WCH cases; 412 SEER cases	Diagnosis age, pT stage, cN stage, nuclear grade and LVI	AUC: 0.876	Nomogram
Wu *et al.* (72)	234	PLR, SCC-Ag, LVI, and pathologic tumour stage (pT stage)	C-index of 0.817 (95% CI, 0.745–0.890)	Nomogram
Hu *et al.* (91)	134	G, LVI, PD-L1, and NLR	C-index: 0.89	Nomogram
Zhu *et al.* (106)	110	T stage, G, LVI and P53 expression	C-index: 0.79	Nomogram
Peak *et al.* (110)	1,636	T stage, LVI, and clinical lymph node status	C-index: 0.880	Nomogram
Zhou *et al.* (111)	75	G, LVI, short diameter of the largest ILN	AUC: 0.948	Nomogram

CS, corpora spongiosa; CC, corpora cavernosa; LVI, lymphovascular invasion; PNI, perineural invasion; G, grade; T, tumour; N, node stage; SCC, squamous cell carcinoma antigen; PLR, platelet-to-lymphoccyte ratio; PD-L1, program death ligand 1; NLR, neutrophil-to-lymphocyte ratio; ILN, inguinal lymph node; AUC, area under the curve; CI, confidence interval; RGS, risk group stratification.

research and large sample data validation, the level of evidence in the literature included in this paper is low. However, the literature still comprehensively analyzes various indicators and provides a lot of literature support. At present, clinicopathological factors, such as the staging and grading of the primary lesion, are still important factors for predicting LNM. These factors are also important components of prediction models, especially nomograms. To date, the exploration of prediction models for LNM has mainly focused on clinicopathological factors or immunohistochemical factors. There is still no unified prediction model, and the prediction value of current models still lacks clinical confirmation in large samples. In addition, because there are many factors included in these prediction models, they are still difficult to evaluate. These deficiencies limit their clinical application. The exploration of noninvasive haematological indicators is one of the important research directions for future preoperative research. The use of single or combined haematological indicators can achieve an accurate prediction before the treatment of the primary tumour and surgery, which will greatly improve the treatment accuracy of patients

and facilitate the rational use of medical resources. At present, the molecular indicators of penile cancer are in the preliminary exploration stage. With increasing cell line construction and molecular mechanism research, molecular indicators will also be potential molecular indicators, but their value still needs further clinical confirmation.

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Footnote

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