

The Factors Predicting the Incidence of Regional Lymph Node Metastases in Patients with Penile Cancer Patients at Prof Dr. I.G.N.G. Ngoerah Hospital Denpasar

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ABSTRACT

Background: Penile cancer is a rare but potentially fatal malignancy, the cause of which is not fully understood. The incidence in Bali shows that from April 1993 to May 2005, there were 72 cases of penile cancer. Penile cancer lymph node metastasis influences the choice of surgical therapy and is also a strong predictor of prognosis. Proper diagnosis and treatment, especially regarding inguinal lymph node metastasis, will affect the prognosis in penile cancer patients. **Objective:** This study aims to prove the existing factors are predictors of the incidence of regional lymph node metastases in penile cancer patients. **Methods:** This study used a retrospective analysis design, with a cohort design to prove the location of the primary tumor, primary tumor size, clinical lymph node palpation, preoperative lymphocyte monocyte ratio (LMR), and tumor histopathological subtype as predictor factors of regional LNM in penile cancer patients. A total of 98 patients and predictor factors were analyzed based on OR and RR values from bivariate and multivariate tests. **Results:** Primary tumor location on the gland and prepuce, positive inguinal lymph node clinical palpation are predictors of LNM incidence in penile cancer patients. While primary tumor size, preoperative LMR value, and histopathological subtype were not associated. **Conclusion:** Many factors are associated with regional LNM in penile cancer which is associated with poor clinical outcomes. The most influential factors are the location of the primary tumor and clinical palpation of inguinal lymph nodes which can be considered as a nomogram to risk stratify patients and determine eligibility for inguinal lymphadenectomy.

Keywords: predictor factors; regional lymph node metastasis; LMR (Lymphocyte monocyte ratio); penile cancer.

INTRODUCTION

Penile cancer is a rare but potentially fatal malignancy. Its cause is not fully understood, but the risk can be eliminated by circumcision at birth. In Indonesia based on the research of Tranggono, et al., it was found that in the period October 1994 to September 2005, at Cipto Mangunkusumo Hospital and Dharmais Cancer Hospital, there were 69 people suffering from penile malignancies. While the data of penile cancer in Bali based on the research of Sastrodihardjo, et al., showed that in the period of April 1993 to May 2005 there were 72 cases of penile cancer.

The standard treatment for primary penile lesions is total or partial penectomy. Standard total/partial penectomy therapy for penile cancer achieves local

control rates above 90% but also causes significant damage, leading to loss of function and psychosexual morbidity. If there are no palpable lymph nodes, the chance of micrometastatic disease is about 25%. Inguinal lymphadenopathy on physical examination shows low positive and negative predictive values. (Hakenberg et al, 2018).

Penile cancer lymph node metastasis influences the selection of surgical therapy and is also a strong predictor of prognosis. Patients with lymph node metastases have been shown to have a worse prognosis. About 80% of men with low-grade penile cancer can achieve prolonged survival, but with increasing levels of lymph node metastasis, survival rates decrease dramatically. (Hakenberg et al, 2018).

Due to the high probability of lymph node dissection, it is crucial to determine candidates for appropriate surgery. However, few studies to date have evaluated risk factors or lymph node metastasis prediction models. Ficarra et al. established the first nomogram to predict lymph node involvement based on a cohort of 265 patients. The clinical stage of inguinal lymph nodes, histological grade, and other pathological features of the tumor were included in the model, and multivariate analysis showed that only lymphovascular invasion and clinically palpable lymph nodes were significant predictors of lymph node status. Recently, a cohort study including 380 penile cancer patients between 2000 and 2010 was conducted to identify predictors of lymph node involvement, multivariable analysis showed that age, pathological stage, and tumor grade were independently associated with lymph node involvement. In addition, the accuracy test of the risk stratification scheme showed that there was no significant difference between different risk group systems.

Proper diagnosis and treatment, especially regarding inguinal lymph node metastasis, will affect the prognosis in penile cancer patients. There are several randomized trials exploring treatment options for penile cancer, but due to the small number of patients, management is usually based on retrospective reviews from large referral centers. As a result, guidelines for treatment, such as those recently published by the European Urological Association, are based on low-level recommendations.

METHODS

This study used a retrospective analysis design, with a cohort design. The population of this study was all penile cancer patients with or without regional lymph node metastases who underwent treatment at Prof. Dr. I.G.N.G. Ngoerah Denpasar Hospital in the period 2018 to 2022 with a total of 98 samples that were in accordance with the inclusion criteria. The inclusion criteria in this study are 1) Penile cancer patients with or without histopathologically confirmed regional lymph node metastases, 2) Penile cancer patients with or without regional metastases who underwent partial or total penectomy for the primary tumor, and underwent dissection or excisional biopsy. The exclusion criteria in this study are 1) Patients with incomplete clinical and histopathologic data in medical records and 2) Penile cancer patients diagnosed less than 6 months from the time of the study. Data analysis was performed using SPSS for Windows version 21.0 software. The statistical analysis included univariate analysis, bivariate analysis, and multivariate analysis.

RESULTS

Characteristics of Research Subjects

Subject characteristics were described based on age, race, sexual history other than wife, circumcision history, primary tumor location, primary tumor size, clinical lymph node palpation, LMR score, tumor histopathology subtype, tumor grading, LVI, and PNI in Table 1.

TABLE 1: Characteristics of Research Subjects.

Characteristics	Incidence of lymph node metastases	
	Positive (n=56)	Negative (n=42)
Age	57,01±13,5	58,59±12,6
Race (n, %)		
Asian	56 (57,1%)	42 (42,9%)
Sexual history other than wife (n, %)		
No	56 (57,1%)	42 (42,9%)
Circumcision history (n, %)		
No	56 (57,1%)	42 (42,9%)
Tumor grading		
Grade I	17 (17,3%)	17 (17,3%)
Grade II	34 (34,7%)	18 (18,4%)
Grade III	5 (5,1%)	7 (7,1%)
Lymphovascular Invasion (LVI)		
Positive	45 (45,9%)	24 (24,5%)
Negative	11 (11,2%)	18 (18,4%)
Perineural Invasion (PNI)		
Positive	27 (27,6%)	11 (11,2%)
Negative	29 (29,6%)	31 (31,6%)
Location of the primary tumor		
Prepuce	22 (22,4%)	13 (13,3%)
Gland	24 (24,5%)	17 (17,3%)
Midshaft	0 (0%)	2 (2%)
Shaft	10 (10,2%)	10 (10,2%)
Tumor size	3,7 ± 0,99	3,4±1,3
Clinical lymph node palpation		
Positive	45 (45,9%)	13 (13,3%)
Negative	11 (11,2%)	29 (29,6%)
Lymphocyte-to-monocyte ratio (LMR)	3,1±2	3,2±1,6

Characteristics	Incidence of lymph node metastases	
	Positive (n=56)	Positive (n=56)
Histopathological subtype of tumor		
High risk	16 (16,3%)	13 (13,3%)
Low risk	40 (40,8%)	29 (29,6%)

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TABLE 2: Relationship between primary tumor location, primary tumor size, clinical lymph node palpation, LMR value, and tumor histopathology subtype on the incidence of lymph node metastases in penile cancer patients.

Characteristics	Incidence of lymph node metastases		RR	CI95%	p-value
	Positive	Negative			
Location of the primary tumor					
Prepuce and gland	46 (60,5%)	30 (39,5%)	1,3	0,81-2,17	0,208
Shaft/corpus	10 (45,4%)	12 (54,6%)			
Primary tumor size					
≥ 3 cm	48 (63,2%)	28 (36,8%)	1,7	0,97-3,098	0,025
< 3 cm	8 (36,4%)	14 (63,6%)			
Inguinal lymph node clinical palpation					
Positive	45 (77,6%)	13 (22,4%)	2,8	1,67-4,75	0,000
Negative	11 (27,5%)	29 (72,5%)			
Preoperative LMR value					
≤ 3	39 (66,1%)	20 (33,9%)	1,5	1,01-2,26	0,028
> 3	17 (43,6%)	22 (56,4%)			
Histopathological subtype of tumor					
High risk	16 (55,2%)	13 (44,8%)	0,9	0,64-1,39	0,798
Low risk	40 (57,9%)	29 (42,1%)			

Table 2 shows the location of the tumor in the prepuce and gland more lymph node metastases (60.5%) compared with negative results of lymph node metastases (39.5%) but these results statistically there is no significant relationship between the location of the primary tumor position with the incidence of lymph node metastases (p=0.208; CI95%: 0.81-2.17) and RR value 1.3. Tumor size > 3cm was found to have more lymph node metastases (63.2%) with p=0.025 and RR value of 1.7, indicating that there is an association between tumor size and the occurrence of lymph node metastases.

Positive clinical palpation was found to have more lymph node metastases (77.6%) with a p-value <0.001 and an RR value of 2.8 indicating that there was a significant relationship between positive clinical palpation and the incidence of lymph node metastases. LMR value <3 Was found to have more lymph node metastases with p=0.028 and RR value of 1.5, indicating that there was a relationship between LMR value and lymph node metastases. The histopathology subtype of the low-risk group was found to have more lymph node metastases with a value of p=0.798 and an RR value of 0.9, meaning that there was no significant relationship between the histopathology subtype and the incidence of lymph node metastases.

TABLE 3: Relationship between tumor grading, LVI, and PNI and incidence of lymph node metastases in penile cancer patients.

Characteristics	Incidence of lymph node metastases		RR	CI95%	p-value
	Positive	Negative			
Tumor grading					
Grade I	17 (50%)	17 (50%)	0,6	0,32-1,02	0,190
Grade II	34 (65,3%)	18 (34,7%)			
Grade III	5 (41,6%)	7 (58,4%)			
LVI					
Positive	45 (65,2%)	24 (34,8%)	1,7	1,24-7,53	0,013
Negative	11 (37,9%)	18 (62,1%)			
PNI					
Positive	27 (71%)	11 (29%)	1,4	1,10-6,23	0,027
Negative	29 (48,3%)	31 (51,7%)			

Table 3 shows that tumor grading grade II was found to have the most positive lymph node metastases (65.3%) with a value of $p=0.190$ which indicates that there is no significant relationship between tumor grading and the incidence of lymph node metastases. LVI and PNI each showed $p<0.05$ which proved that LVI and PNI were associated with the incidence of regional lymph node metastases.

The significance values of the variables of tumor location, tumor size, clinical lymph node feeling, LMR, histopathology grading, LVI, and PNI are lower than 0.25, so these variables can be included as multivariate model candidates.

In addition, the significance value of the histopathology subtype variable was more than 0.25, so the variable was excluded from the multivariate model test.

Multivariate analysis uses a logistic regression test because all data in the variables are categorical. The omnibus test results obtained data p value $0.000 < 0.05$ and the results of the Hosmer and Lameshow test obtained a p-value $858 > 0.05$ means that this test model is fit for use. The classification table obtained 76.5%, which means that the test model used in predicting the independent variable on the dependent variable is 76.5%. The final results of the variables in the equation (Table 3).

TABLE 4: Tumor location, size, tumor lymph node clinical palpation and LMR as predictors of lymph node metastases in penile cancer patients.

Variable	B	OR	CI95%	p-value
Tumor location on gland and prepuce	1,29	3,6	1,04-12,60	0,042
Tumor size ≥ 3 cm	1,12	3	0,73-12,94	0,124
Clinical palpation of positive inguinal lymph nodes	2,56	13	3,8-44,66	0,000
LMR ≤ 3	0,76	2,1	0,70-6,53	0,179
Histopathology grading grade III	0,79	2,2	0,93-5,28	0,070
LVI positive	1,33	3,7	0,98-14,62	0,053
PNI positive	0,35	1,4	0,42-4,78	0,564

Table 4 shows that tumor location, tumor size, and clinical lymph node LMR, grade, LVI, and PNI have positive B values, which means that there is a positive relationship between tumor location, tumor size, clinical lymph node LMR, histopathology grading, LVI, and PNI on the incidence of lymph node metastases in penile cancer patients. Clinical lymph node sensing has a dominant influence ($p=0.000$) on the occurrence of lymph node metastases compared to tumor location ($p=0.042$) and both have a relationship as a predictor model, while tumor size ($p=0.124$), LMR ($p=0.179$), grading ($p=0.070$), LVI ($p=0.053$), and PNI ($p=0.564$) are not related to the predictor model. Clinical lymph node palpation had an Adj OR value of 13 (CI 95%: 3.8-44.66). The results of multivariate analysis can be concluded that clinical lymph node sensing has a dominant influence on the incidence of lymph node metastases in penile cancer patients.

DISCUSSION

Description of incidence of lymph node metastases in penile cancer patients

The results showed that the mean age of penile cancer patients who experienced lymph node metastases was 57.01 years (SD: 13.5) while those who did not experience lymph node metastases were 58.59 years (SD: 12.6). Research by Tranggono, et al., found that the age range of patients was around 40-50 years with the prevalence of the most common tribes, namely Chinese, Betawi, and Batak. The incidence of penile cancer increases with age. The peak age is during the sixth decade of life, but about 20% of all new cases occur in men younger than 50 years (Chaux et al., 2013).

The average age of penile cancer patients is 54.5 ± 14.6 years (Harmaya et al., 2017). Research by Tan et al (2019) found a higher median age of penile cancer patients, namely 65.1 years. Research by Wang et al (2018) found the median age of penile cancer patients was 53 years.

There are a number of studies showing that the incidence of lymph node metastasis in penile cancer patients may vary based on various factors, including patient age, tumor size, and clinical examination results. In a study conducted by Chaux et al. (2013), it was reported that the incidence of penile cancer tends to increase with age, with the peak incidence occurring in the sixth decade of life. Nonetheless, about 20% of these penile cancer cases occur in men younger than 50 years, suggesting that penile cancer is not only limited to the older age group.

Patients with Asian race and those with lymph node metastases are more than those without lymph node metastases. Penile cancer is a typical tumor of non-industrialized countries with an incidence 20-30 times higher in Africa and South America (Aniello et al., 2020). The incidence of penile cancer is also influenced by race and ethnicity, with the highest incidence in white Hispanics (1.01/100,000) compared to Alaskans, and Native Americans. Indians (0.77/100,000), blacks (0.62/100,000), and non-Hispanic whites (0.51/100,000). Other regions of the world, such as South America, Southeast Asia, and parts of Africa, have much higher incidences, representing up to 1-2%. Penile cancer is common in areas with a high prevalence of human papillomavirus (Hakenberg et al., 2015).

All patients were found to have no history of sexual intercourse other than wife (100%) and all patients were found to have never performed circumcision (100%). Research by Tranggono, et al found that penile cancer was mostly found in patients who were not circumcised (47.8%). Research by Tan et al (2019) also found a higher incidence of penile cancer in patients who were not circumcised (92.3%). Circumcision is a practice that has existed since long before human history as one of the most common additional procedures performed worldwide. It is usually performed to treat underlying physiological phimosis or pathological phimosis caused by traumatic injury or balanitis xerotica obliterans, refractory balanoposthitis, chronic, recurrent urinary tract infections (Emmanuel & Eng, 2019; Morris et al., 2012).

The location/position of the tumor with the incidence of lymph node metastases is more commonly found with the location in the penile gland (24.5%). Similar results were also found in the study (Borque-Fernando et al., 2023) that the most tumor locations were found in the gland area (63.6%) while Tan et al's study (2019) found that the most common location of penile cancer was in the prepuce and penile gland (74.4%). Tranggono et al's study found that the location of the primary lesion was most common in the glans and shaft and least in the sulcus coronarius, where most patients were found in stages T1 and T2 (63.9%), stages N2-3 as much as 47.8% and M1 as much as 6.3%. The presence of prepuce in penile cancer is rarely seen in uncircumcised men (Dilek et al., 2019). Penile squamous cell carcinoma is the dominant histologic type of penile carcinoma (Li et al., 2019; Mentrikoski et al., 2014).

The results showed that the mean tumor size was 3.7 cm (SD: 0.99) in the group with lymph node metastases. Research by Zheng et al (2021) found the distribution of tumor size was mostly 3 cm 52.3%, and 47.7% of tumors were more than 3 cm in size. When tumor size was entered into a competing risk regression model as a categorical variable, suggesting that penile cancer patients with tumors >3 cm were more likely to experience cancer-specific mortality (Zheng et al., 2021).

Positive clinical lymph node palpation was found to have more lymph node metastases (45.9%). The same research results were also found in the study of Tan et al (2019) where clinical palpation of lymph nodes was found to be higher (79.5%). Careful palpation of both groins to assess for enlarged lymph nodules is part of the initial physical examination in patients suspected of having penile cancer (Hakenberg et al, 2018). If there are lymph nodules that are not palpable, there is a 25% chance of micrometastasis. Imaging studies are not very helpful in clinically staging the inguinal region. There are options that may be used in obese patients where palpation is not reliable (Hakenberg et al, 2018; Lau et al., 2015).

The results showed that the mean lymphocyte monocyte ratio was found to be the same mean (3.1) lower than the negative results of lymph node

metastases. Research by Ma et al (2021) found an average LMR of 2.26 in other cancer cases such as colon, breast, and bone cancer.

The results showed that the low-risk histopathology subtype was found to have more lymph node metastases (40.8%). Research by Wang et al (2018) found the most histopathological subtype of SCC was lymph node metastases (58.2%). Grade II was found to have more lymph node metastases (34.7%) in this study. In line with the research of Tan et al (2019) who found that most penile cancer patients with grade II (43.6%). Research by Wang et al (2018) found a grade II of 73.6%. Different results found that patients with penile cancer are dominant with clinical stage III (53.3%) with a dominant histological picture of keratinizing squamous cell carcinoma (63.3%) (Harmaya et al., 2017).

Results based on positive vascular lymphocyte invasion found more lymph node metastases (45.9%). Research by Wang et al (2018) found vascular lymphocyte invasion of (83.3%). Negative perineural invasion was found to have more lymph node metastases (29.6%). Research by Wang et al (2018) found a negative perineural invasion of (57.1%). Lymph node metastasis is the most important prognosis factor for patients with penile cancer. Although more than 50% of patients with SCC have no palpable inguinal nodes at the time of examination about 20% still harbor hidden micrometastases <2 mm in this location (Hadway et al., 2014). The results of the study (Jindal et al., 2021) found that grade II was most commonly found (66.67%) with LVI at 34.78%, and PNI at 37.68%. A total of 52.17% found inguinal lymph node metastases.

Primary tumor location on the incidence of regional lymph node metastases in penile cancer patients

The results showed that the location of the primary tumor position was not independently associated with the incidence of lymph node metastases ($p=0, 208 > 0.05$) but the results of multivariate analysis showed that the location of the primary tumor was associated with the occurrence of lymph node metastases and was a predictor factor that increased the occurrence of lymph node metastases ($p=0.042$). Patients with tumor location in the penile gland are more likely to experience lymph node metastasis compared to skin or glandular tumors and the tumor location is an independent prognostic factor that should be considered during clinical management (Li et al., 2022).

Research on the relationship between primary tumor location in penile cancer and lymph node metastasis suggests that tumor position may influence the pattern of lymphatic spread. Graafland et al. (2010) identified that tumors located in the glans penis have a higher risk for metastasis compared to tumors located in the prepuce.

The findings of Graafland et al. (2010) were reinforced by a study conducted by Qu et al. (2018). They found that tumor size was also an important

factor in the risk of lymph node metastasis, with tumors measuring more than 3 cm having a higher risk compared to tumors measuring 3 cm or less.

Primary tumor size on the incidence of regional lymph node metastases in penile cancer patients

The results of this study found an independent relationship between tumor size and the incidence of lymph node metastases. Research (Li et al., 2022) found that tumor size ≥ 3 cm was associated with the survival of penile cancer patients ($p = 0.001$). A prospective study involving 106 patients also found that high tumor grading, LVI, and clinical palpation were positively associated with tumor metastases (Aniello et al., 2020; Ficarra et al., 2005). Zheng et al's (2021) study showed tumors > 30 mm were significantly associated with an increased likelihood of lymph node metastasis compared to tumors ≤ 30 mm (OR = 1.46, 95%CI: 1.03-2.07, $P = 0.034$). Consistent with the findings Chalya and colleagues identified 236 penile cancer patients from a medical center in Tanzania, of whom 154 patients had lymph node metastases at diagnosis.

Tumor size is one of the staging criteria for many cancers. In penile cancer jerseys, primary tumor volume has prognostic significance in some studies. Tumor size is also related to nodal status, with increasing tumor diameter associated with an increased rate of nodal metastasis, where outcomes with the same number of positive lymph nodes will have decreased survival with increasing tumor size, with increasing tumor size and primary tumor location as significant predictors. Tumor size above 3 cm was significantly associated with an increased risk of lymph node involvement. (Wang et al, 2018).

Clinical palpation of lymph nodes on the incidence of regional lymph node metastases in penile cancer patients

The results showed that positive clinical feeling was significantly associated with the occurrence of lymph node metastases and positive clinical feeling was a predictor factor that increased the occurrence of lymph node metastases. The results of multivariate analysis showed that clinical lymph node feeling had a dominant influence on the incidence of lymph node metastases in penile cancer patients. Similar results were also found in the research of Wang et al (2018) that positive clinical feeling was associated with the occurrence of lymph node metastases. Lymph node enlargement is highly suggestive of metastasis. On physical examination, the number of palpable nodules on each side should be recorded and the mobility of the nodules assessed (Hakenberg et al., 2018; Lau et al., 2015). Research by Tan et al (2019) found that out of 8 patients with clinical lymph node palpation 4 people died after a year. This suggests that lymph node metastases are the only significant risk factor associated with worse recurrence survival and cancer-specific survival.

Research conducted by Agrawal et al. (2008) showed that the presence of positive lymph node palpation results was strongly associated with the discovery of metastases histopathologically.

These findings underscore the importance of palpation as an initial step in the clinical evaluation of patients with penile cancer.

The risk of micrometastasis in clinically nonpalpable glands is close to zero for low-risk tumors increasing to 25% in high-risk patients. For intermediate-risk patients, the chance of micrometastasis is about 10%. In patients with palpable inguinal lymph nodes, the risk of metastatic spread is much higher and can reach 70% in the high-risk prognostic group. Therefore, careful clinical examination and radiologic staging are mandatory in the management of inguinal nodes in penile cancer (Chaux et al., 2013).

Preoperative lymphocyte monocyte ratio (LMR) value on the incidence of regional lymph node metastases in penile cancer patients

The results of the study found that LMR values were independently associated with lymph node metastases and low LMR values were found to have more lymph node metastases. Research by Jindal et al (2021) found that the incidence of LMR < 3 was 59.42% and LMR was a risk factor for inguinal lymph node metastases. These results are in line with the research of Tan et al (2019) that patients with low LMR (< 3.3) have a much higher stage, recurrence survival, and worse cancer-specific survival compared to high LMR so that LMR can be a biomarker for penile cancer prognosis.

LMR, the ratio of lymphocytes to monocytes, is a comprehensive index that can better predict the long-term prognosis of cancer patients. LMR is reported to have prognostic value in several malignancies. High LMR was associated with poor OS in previous reports, and LMR can be considered a potential surrogate biomarker in various cancers. Although the mechanism of the association between higher LMR and worse prognosis has not been fully clarified, LMR might reflect the balance between the beneficial role of lymphocytes and the unfavorable effect of monocytes with respect to cancer progression. A higher LMR indicates lower lymphocyte or higher monocyte levels in the peripheral blood of cancer patients. Lymphocytes play an important role in defense against cancer cells by inducing cytotoxic cell death and suppressing tumor cell proliferation and migration. Many types of lymphocytes, such as T cells, dendritic cells, monocytes, and macrophages, have been shown to infiltrate cancer (Y et al, 2008; Lavin et al, 2015).

Tumor-infiltrating lymphocytes form a defense barrier against the spread of cancer. Therefore, a decrease in the number of lymphocytes in the blood and tumor stroma leads to the downregulation of the immune response to the tumor. Moreover, a decrease in the number of lymphocytes in the blood has been identified as an independent prognostic factor in various cancers. In addition, peripheral blood monocyte counts prior to treatment have been shown to correlate with poor prognosis in patients with various cancers.

Upon recruitment into tumor tissue, monocytes differentiate into tumor-associated macrophages (TAMs) (Kitamura et al, 2015).

Tumor histopathology subtypes on the incidence of regional lymph node metastases in penile cancer patients

Histopathology subtype found no significant relationship between histopathology subtype and the occurrence of lymph node metastases. Different results were found in the study (Wang et al., 2018) that histopathology was associated with the occurrence of lymph node metastases and histopathology subtype became the most dominant risk factor for lymph node metastases with a hazard ratio of 28.74 times. To assess the risk of ILNM, SCC subtypes were classified as three groups according to the European Association of Urology (EAU) guidelines. The low-risk group included verrucous, papillary, and warty types. The intermediate-risk group includes common squamous cell carcinoma (SCC) and mixed forms. High-risk SCC variants are basaloid, sarcomatoid, adenosquamous, and poorly differentiated types. (Hakenberg et al, 2018).

Penile cancer spreads mainly through the lymphatic system to the inguinal and pelvic lymph nodes. (Dillner et al, 2000) The incidence of lymph node metastases is the most important prognostic factor for recurrence, metastasis and survival in these patients. There are many pathologically-based factors that have been shown to be important in relation to the rate of ILNM. (Cubilla, 2009), (Sanchez et al, 2015) However, the relationship between histopathologic subtype classification and ILNM remains uncertain with limited data. There are several advantages to assessing the histopathological classification of tumors, including (1) identifying morphological patterns etiologically associated with specific causative factors and (2) biologically identifying tumor subtypes with distinctive morphologies associated with good or poor prognosis. (Wang et al., 2018)

CONCLUSIONS

Primary tumor location in the gland and prepuce and positive inguinal lymph node clinical palpation were predictors of regional lymph node metastases in penile cancer patients, while primary tumor size > 3cm, lymphocyte monocyte ratio (LMR) value ≤ 3 and high-risk tumor histopathology subtype were not predictors of regional lymph node metastases in penile cancer patients.

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