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Survival Analysis of Primary Tumor Staging (T), Lymph Node Status (N), Tumor Grading, Cell Subtype, Lymphovascular Invasion Status, and Preoperative Neutrophil-Lymphocyte Ratio Values in Penile Cancer

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ABSTRACT

Background: Penile cancer is rare but has a major impact on patients and health workers in its management. In penile cancer, tumors can grow anywhere in all parts of the penis, starting from the glans penis, foreskin, and shaft of the penis, which can spread and damage the surrounding tissue structures such as the pubic bone, scrotum, and others. No studies specifically analyze the survival of penile cancer. ***Aim:*** This study assessed the relationship between primary tumor staging, lymph node status, tumor grading, cell subtype, lymphovascular invasion (LVI), and preoperative neutrophil-lymphocyte ratio (NLR) on the survival of penile cancer patients. ***Material & Methods:*** This study was a survival analysis study with a retrospective cohort design. Primary tumor staging (T), lymph node status (N), tumor grading, cell subtype, LVI status, and preoperative NLR values are independent variables included. The dependent variables are survival time and mortality. Descriptive analysis, Kaplan-Meier curve analysis, and Cox Proportional Hazard Regression test were performed. ***Results:*** Eighty (80) subjects with a mean age of 55.71 ± 12.45 years old. Forty-one percent of the subjects died with a mean survival time of 60.65 months (95% CI 51.25-70.04). Cox proportional hazard regression analysis showed that staging N3 and the condylomatous subtype at the time of diagnosis increased the risk of mortality with a hazard ratio (HR) of 3.55 (95% CI 1.03 – 12.31) and 6.77 (95% CI). 1.02 – 44.85), respectively. ***Conclusion:*** Lymph node staging N3 and condylomatous subtype were factors with poorer survival prognosis.

Keywords: penile cancer; survival; penile cancer staging; tumour subtype; hazard ratio

INTRODUCTION

Penile cancer develops in the skin or tissue of the penis. This cancer is rare but has a major impact on patients and health workers in its management. Tumors in the penis include types of pre-malignant tumors and malignant tumors. Malignant tumors of the penis are mostly squamous cell carcinoma, accounting for 95 percent of cases.[1]

Based on data from EAU in 2018, the incidence of penile cancer in Western countries is rarer than in developing countries. Cases of penile cancer occurred in 1 in 100,000 men in America in 2000. This figure has decreased in the 2014 report to 0.4-0.6 per 100,000 men. In some developing countries such as South America, Southeast Asia, and parts of Africa, the incidence is much higher and accounts for as many as 1-2% of cancers in men. The annual incidence according to age in India is 0.7 to 3.0, in Brazil 8.3 (each per 100,000), and even higher in Uganda, where penile cancer is the most frequently diagnosed cancer in males.[2]

Meanwhile, in Indonesia, data from Cipto Mangunkusumo Hospital and Dharmais Cancer Hospital for 12 years (1994-2005) found 69 cases of penile carcinoma or 6.3 cases per year.[3]

Data at the Prof. Dr. I.G.N.G. Ngoerah Hospital in Denpasar itself recorded 65 patients diagnosed with penile cancer for 5 years (2011-2015), with an average patient age of 53.24 ± 13.42 years.[4] However, in developing countries with good health and religious systems and embracing the importance of circumcision for health, the incidence rate of malignancy of the penis is 0.1 per 100,000.[5]

There are several risk factors for penile cancer, such as phimosis, penile hygiene standards, number of sexual partners, HPV virus infection, exposure to tobacco products, and inflammatory processes such as Lichen Sclerosus, Balanitis Xerotica Obliterans, and Carcinoma In Situ. Phimosis is found in 25-75% of penile malignancies. Circumcision in the neonatal period and in children is a preventive factor for penile cancer because it eliminates the closed environment at the foreskin, the most common location for penile cancer.[6]

Several studies have assessed the impact of penile cancer on the psychological condition of patients, both before and after receiving treatment. Matters affected by penile cancer include the patient's sexual life (sexual activity, sexual health, sexual organ cosmetics, erectile dysfunction), satisfaction with treatment, and mental disorders such as anxiety and depression. One study conducted by Sosnowski et al., which assessed the quality of life (Quality of Life) and Health-Related Quality of Life (HRQoL) in penile cancer patients who received treatment with total penectomy and was assessed by the EORTC QLQ C30 questionnaire, obtained median results in the individual domain is lower than the median outcome of other genitourinary cancer patients that occur in males (50:66,7).[7]

In penile cancer, tumors can grow anywhere in all parts of the penis, starting from the glans penis, foreskin, and shaft of the penis, which can spread and damage the surrounding tissue structures such as the pubic bone, scrotum, and others. The spread of these tumor cells can continue to locoregional lymph nodes and metastasize to other organs such as the liver and lungs. Increasing the stage of penile cancer will increase patient morbidity and mortality, which will affect the prognosis of penile cancer patients themselves.[2] The prognosis of penile cancer can be determined by several factors, such as clinical stage, tumor grade, cell subtype, regional lymph node metastases, lesion location, and several other chemical parameters.[8] Related to the prognosis is closely related to the assessment of survival in the form of Overall Survival (OS), Cancer-Specific Survival (CSS), or Disease-Free Survival (DFS). Each of these predictor factors has a different prognostic value.[9]

Previous research showed that clinical staging cT1-cT2 and cN1 had Disease Free Survival (DFS)-5 years of 80.34% and Overall Survival (OS) of 72.22%, and these survival rates tended to decrease with increasing staging. (Suh et al., 2014). Tumor grading is also said to affect the survival of penile cancer patients. According to a study conducted by Aita, G.A. et al. (2016), it was reported that high-grade classification was a predictor factor for overall survival and cancer-specific survival in penile cancer patients, with a relative risk of 14.8 times compared to low and intermediate-grade (p= 0.019).[10] In addition, several studies comprehensively examine the relationship between tumor morphology and prognosis based on histological subtypes of penile cancer. The reported prognostic value is the mortality rate of penile cancer patients based on histological subtypes, summarized in a systematic review by Sanchez et al. (2015).[11]

Several histological subtypes have been reported, such as SCC, verrucous, papillary NOS, pseudohyperplasia, cubiculum, warty, basaloid, sarcomatoid, and mixed types. The basaloid subtype has the highest mortality rate compared to the other subtypes, with a 5-year overall survival of 50%.[11] The presence of lymphovascular invasion is a poor prognostic indicator in various types of malignancy. In a study conducted by Li et al., a worse prognosis was obtained in conditions of positive lymphovascular invasion, which was assessed for both 3-years OS and Penile Carcinoma-Specific Survival (PCSS) of 48.6% and 68.5% ($p<0.001$), when compared with negative lymphovascular invasion conditions.[12] An increase in the neutrophil-lymphocyte ratio (NLR) is associated with an increase in the secretion of pro-inflammatory cytokines that trigger DNA damage that can worsen the prognosis of penile cancer patients.[13]

Several studies have begun to analyze the effect of predictive factors such as primary tumor staging, lymph node status, tumor grade, tumor cell subtype, lymphovascular invasion, or neutrophil-lymphocyte ratio, on the survival of several types of cancer, such as breast cancer, cervical cancer, ovarian cancer, etc. However, no studies specifically analyze the survival of primary tumor staging factors, lymph node status, tumor grading, cell subtypes, lymphovascular invasion, and preoperative neutrophil-lymphocyte ratio in penile cancer patients, especially in Bali. Based on the description above, further research will be carried out regarding the survival analysis of the above factors in penile cancer patients. This study aimed to determine the effect of primary tumor staging, lymph node status, tumor grade, Penile Squamous Cell Carcinoma (SCC) subtype, Lymphovascular Invasion, and preoperative value of Neutrophil-Lymphocyte Ratio on penile cancer survival.

MATERIALS AND METHODS

This research is a survival analysis study with a retrospective cohort design. This research was conducted by observing penile cancer patients when they were diagnosed until a certain period, according to the last examination record in the medical record. The research will be conducted at the Department of Urology, Faculty of Medicine, Udayana University / Prof. Dr. I.G.N.G Ngoerah Hospital in February 2022. Sampling was carried out at the Urology Poly at Prof. Dr. I.G.N.G Ngoerah Hospital.

The data used in this study is secondary data obtained from medical records of patients with penile cancer undergoing treatment at Prof. Dr. I.G.N.G Ngoerah Hospital from 2015-2021. The sample in this study was taken through total sampling. Then the subjects of penile cancer patients who met the inclusion and exclusion criteria were selected as samples. The inclusion criteria included penile cancer patients aged over 18 years; Penile cancer patients who come for treatment at the Urology polyclinic at Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar. Exclusion criteria included patients with incomplete clinical and histopathological data on medical records; Penile cancer patients with 1 or more comorbidities. Comorbidity is the presence of one or more additional conditions that occur simultaneously or have been suffered by the patient before experiencing penile cancer. These comorbidities can be systemic diseases such as heart disease, diabetes mellitus, hypertension, and/or autoimmune diseases; Penile cancer patients were diagnosed less than 6 months after the study.

The independent variables in this study were primary tumor staging (T), lymph node status (N), tumor grading, cell subtype, LVI status, and preoperative NLR values.

The dependent variables in this study were survival time (T) and patient sensor status, which indicated whether a failure or event occurred while the study was in progress (d). *Control variables* are controlled by design and analysis because their presence can interfere with the relationship between the independent and dependent variables. The variables controlled by design were comorbidities, and the variables controlled by the analysis were the patient's age, stage of metastases (M), and type of therapy. Data analysis in this study consisted of descriptive analysis, bivariate Kaplan-Meier analysis, and multivariate analysis with Cox proportional hazard regression. Data analysis will be performed using SPSS software version 23.0

RESULTS

This study involved 80 subjects of penile cancer patients. Of these, 41.2% died, and the remaining 58.8% were still alive as of 28 February 2022. The average length of survival obtained from the Kaplan-Meier descriptive analysis was 60.65 (95% CI 51.25 – 70.04) months. 2-year survival in subjects was found to be 51%. The subjects' age distribution was normal in the Kolmogorov-Smirnov test ($p > 0.05$), so the data are presented as the mean and standard deviation. The mean age of the subject patients was 55.71 ± 12.45 years. This distribution indicates the average age of penile cancer patients in middle age. The long-treated distribution was also found in the normal distribution. Meanwhile, the NLR values were found to have an abnormal distribution ($p < 0.05$) with a median of 3.97 (IQR 2.35 – 7.76) (Table 1).

TABLE 1: Basic patient characteristics subject.

Variable	n= 80 (mean ± SD/ %)
Age (years), mean ± SD	55.71 ± 12.45
Length of survival (months) mean (95% CI)	60.65 (51.25 – 70.04)
NLR, median (IQR)	3.97 (2.35 – 7.76)
Output, n (%)	
Life	47 (58.8)
Die	33 (41.2)

The clinical characteristics of the subject's cancer are described based on the T, N, and M stages; grading characteristics; and the distribution of subtypes from histopathological results. Of the 80 subject patients, 51.3% had penile cancer with stages T1 and T2, while the remaining 48.7% had penile cancer with stages T3 or T4. Likewise, with the distribution of stage N, as many as 47.5% of subjects suffered from penile cancer stages N2 to N3. Meanwhile, 22.5% of patients had penile cancer with the M1 stage.

This distribution shows that the average patient has penile cancer with a fairly progressive disease condition (Table 2).

The histopathological examination found that most patients had moderately differentiated cancer, in which 46.3% were found to be grade 2. The most common type of cancer found was the usual SCC subtype, 91.3% of the subject patients. In addition, 36.3% of the sample was found to be positive for LVI (Table 2).

TABLE 2: Characteristics of tumors in patient subjects.

Variable	Total
Tumor,n(%)	
1	18 (22.5)
2	23 (28.8)
3	30 (37.5)
4	9 (11,3)
Nodul,n(%)	
0	30 (37.5)
1	12 (15.0)
2	16 (20.0)
3	22 (27.5)
Metastase N (%)	
0	62 (77.5)
1	18 (22.5)
LVI, n (%)	
Negative	51 (63.7)
Positive	29 (36.3)
Grading, n (%)	
1	34 (42.5)
2	37 (46.3)
3	9 (11,3)
Subtype, n (%)	
Usual SCC	73 (91.2)
Condylomatous SCC	5 (6,3)
Verrucous SCC	2 (2,5)

Each subject patient who participated in this study was carried out by tracing the history of the type of therapy. In the surgical history, it was found that most of the subject patients had undergone partial surgery and/or total penectomy of 91.3%.

In addition, most of these patients had undergone inguinal lymph node dissection surgery, which was 75%. In the history of chemotherapy, it was found that not all subject patients underwent chemotherapy.

There were 13.8% of patients who received TIP neo-adjuvant chemotherapy only, 32.5% of patients received TIP adjuvant chemotherapy only, and 7.5% of patients received a combination of neo-adjuvant chemotherapy and TIP adjuvant regimen.

In contrast, 46.3% of patients did not undergo chemotherapy at all. None of the penile cancer patients in this study underwent radiotherapy. As many as 36.3% of the sample in this study received combination therapy, namely primary tumor surgery, KGB dissection, and chemotherapy, with a median initiation of combination therapy starting 2.13 (IQR 1.12 – 7.13) months after diagnosis (Table 3).

The effect of the type of therapy on survival, a Kaplan-Meier bivariate analysis was performed on each type of therapy given to penile cancer patients. The variable combination of neo-adjuvant and adjuvant chemotherapy was found to be significantly related to survival and duration of survival in penile cancer patients with a median survival of 51.51 months (95% CI 32.12-70.90) with a p<0.05 (Table 4).

TABLE 3: Characteristics of the type of therapy in the subject patient.

Variable	Total
Chemotherapy	
Neo-adjuvant chemotherapy only, n (%)	11 (13,8)
Adjuvant chemotherapy only, n (%)	26 (32.5)
Neoadjuvant and Adjuvant Chemotherapy, n (%)	6 (7.5)
No Chemotherapy, n (%)	37 (46.3)
Primary tumor surgery, n (%)	
Not operated on	7 (8,8)
Partial Penectomy	7 (8,8)
Total Penectomy	66 (82.5)
Inguinal Lymph Node Dissection, n (%)	
No	20 (25)
Yes	60 (75)
Combination of surgery and chemotherapy, n (%)	
Yes	19 (23.8)
No	61 (76.3)
Initiation of combination therapy (months) (n = 19) median (IQR)	2.13 (1.12 – 7.13)

Table 4: Results of Kaplan Meier analysis for the variable control type of therapy.

Variable	Longevity (months) Average (95% CI)	Log Ranks (p)
Chemotherapy (TIP Regimen)		
Neoadjuvant only	37.00 (18.15-55.86)	
Adjuvant only	29.08 (23.14-35.01)	
neo-adjuvant + adjuvant	51.51 (32.12-70.90)	*0.040
No chemotherapy	72.19 (59.76-84.62)	
Operation		
Not operated on	55.55 (20.10-91.01)	
Partial penectomy	43.91 (22.42-65.39)	0.738
Total penectomy	57.85 (48.73-66.98)	
Inguinal Lymph Node Dissection		
No	48.87 (28.62-69.14)	0.054
Yes	60.49 (51.14-69.83)	

Before bivariate analysis using the Kaplan-Meier test, identification of the cutoff points for sample categorization based on the NLR value was performed. ROC analysis was performed to identify the optimal NLR cut point for identifying mortality in penile cancer patients.

The results of the ROC analysis found that the NLR value could not significantly predict mortality with an area under the curve (AUC) value of 0.573 (95% CI 0.443 – 0.703) and a p-value> 0.05 (Figure 5.1). The Youden index analysis identified the optimal NLR cut point for predicting mortality at 4.3855. The sample dichotomy with the intersection points found that 43.8% of respondents had NLR values ≥ 4.3855 (Table 5).

TABLE 5: ROC analysis results for NLR values and mortality.

Variable	AUC (95% CI)	P	Cut Point	Sensitivity	Spesivity
NLR	0.573 (0.443 – 0.703)	0.272	4.3855	57.6%	66.0%

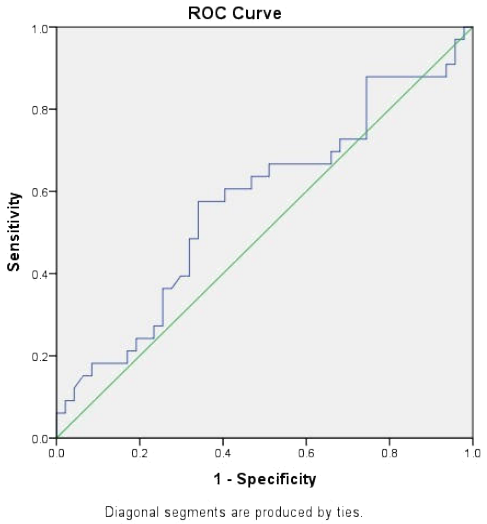

FIGURE 1: ROC curve for NLR and mortality.

Bivariate analysis was performed using the Kaplan-Meier test for each independent variable. As for the 6 independent variables analyzed with the Kaplan-Meier test, 4 variables were significantly related to the survival and duration of survival in penile cancer patients. The four variables significantly related are stage T, stage N, NLR values, and LVI. The histopathological characteristics of cancer tissue, including subtype and grading of penile cancer tissue, were not significantly related to survival in bivariate analysis (Table 6).

Staging, node and LVI were independent variables with the largest effect sizes in the bivariate Kaplan-Meier analysis.

Penile cancer patients with negative LVI had a median survival of 74.17 (95% CI 63.39 – 84.96) months, while patients with positive LVI had a median survival of 36.78 (95% CI 25.01 – 48.55) months. In addition, patients with stage N0 were found to have an average length of survival of 79.01 (CI 66.09-92.10) months, compared to patients with stage N3, which was 27.54 (CI 18.83-36.26) months (Table 6). Meanwhile, the NLR value was found to have a relatively small effect size with an average survival rate of 68.62 (95% CI 56.44 – 80.79) months in the high group and 45.64 (95% CI 33.69 – 57.60) months in the low group (Table 6).

TABLE 6: Results of the Kaplan-Meier survival analysis.

Variable	Length of Survival (Months) Average (95% CI)	Log Rank (p)
***staging* Q**		
1	86.85 (73.18-100.52)	
2	57.34 (43.25-71.43)	0.009*
3	46.46 (32.77-60.14)	
4	30.83 (12.34-49.31)	
***staging* N**		
0	79.01 (66.09-92.10)	
1	65.49 (47.88-83.12)	<0.001*
2	57.05 (37.04-77.07)	
3	27.54 (18.83-36.26)	
Pre-Operational NLR		
< 4.3855	68.62 (56.42-80.78)	0.041*
≥ 4.3855	45.64 (33.69-57.60)	
Lvi		
Negative	74.17 (63.39-84.95)	<0.001*
Positive	36.78 (25.01-48.55)	
Grading		
1	70.45 (56.57-84.34)	
2	51.59 (39.49-63.69)	0.150
3	40.83 (51.25-70.04)	
subtype		
SCC	59.45 (49.58 – 69.32)	0.467
Non-SCC (Condylomatou, verrucous)	65.58 (43.43 – 87.74)	

*p < 0.05.

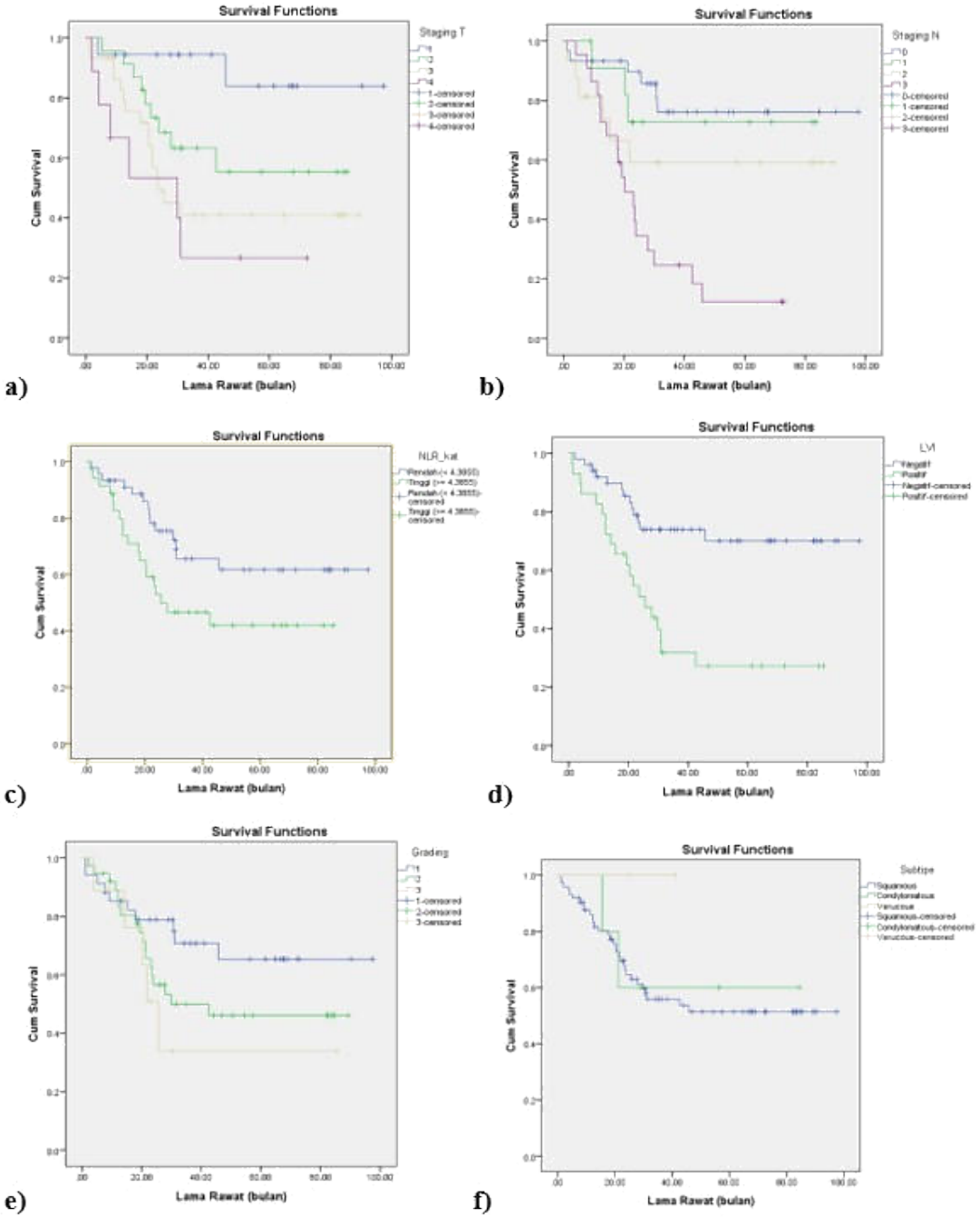

FIGURE 2: Survival curves for T (a), N (b), NLR (c), LVI (d), grading (e), and SCC (f) subtypes.

Further analysis was performed using a multivariate Cox regression test to identify significant and independent determinant factors for survival in penile cancer patients. In addition to the independent variables, Cox's regression also controlled for the effects of potential confounders such as age, metastases, and the combination of therapy the patient was receiving.

Only 2 of the 6 independent variables studied in this study were found to be significantly and independently related to survival based on the results of the multivariate Cox regression test. Those variables are stage N and subtype. Penile cancer patients with stage N3 at the time of diagnosis were found to have an increased risk of mortality with a hazard ratio (HR) of 3.55 (95% CI 1.03 – 12.31).

Meanwhile, patients with penile cancer subtype condylomatous also experienced an increased mortality risk with HR 6.77 (95% CI 1.02 – 44.85) compared to patients with the usual SCC subtype. As for one of the confounding variables, a combination of operative therapy and chemotherapy was also significantly and independently associated with mortality. After statistical adjustment for the time of initiation of therapy, the combination of operative therapy and chemotherapy was found to be associated with mortality ($p < 0.05$) but with a very small effect size (Table 7).

TABLE 7: Multivariate Cox regression test results.

Variable	Hazard Ratio (95% CI)	P
Age (every 1 year)	1.01 (0.98 – 1.05)	0.396
Combination therapy (surgery and chemotherapy) (with time dependency adjustment)		
No	1	0.037*
Yes	1.00 (1.00 – 1.00)	
Metastases		
0	1	0.201
1	1.98 (0.70 – 5.60)	
Tumor		
1	1	
2	0.86 (0.13 – 5.49)	0.856
3	2.92 (0.54 – 15.99)	0.216
4	2.53 (0.39 – 16.56)	0.334
Nodul		
0	1	
1	1.29 (0.26 – 6.29)	0.544
2	2.65 (0.70 – 10.06)	0.151
3	3.55 (1.03 – 12.31)	0.046*
Pre-Operational NLR		
< 4.3855	1	0.139
≥ 4.3855	1.91 (0.81 – 4.50)	
Lvi		
Negative	1	0.148
Positive	1.88 (0.80 – 4.44)	
Grading		
1	1	
2	1.37 (0.52 – 3.62)	0.524
3	1.24 (0.36 – 4.26)	0.734
subtype		
Usual SCC	1	
Condylomatous SCC	6.77 (1.02 – 44.85)	0.047*
Verrucous SCC	N/A	

*p < 0.05.

DISCUSSION

A total of 80 penile cancer patients were recruited as research subjects through total sampling. The mean age of the subjects was 55.71 ± 12.45 years. Based on the staging of the spread of cancer, 48.7% of subjects were found to have staged T3 or T4 cancer at the time of diagnosis, 47.5% were found to be staged N2 to N3, while 22.5% were found to have metastases (M1). These findings indicate that at least half of patients with penile cancer are diagnosed with cancer that has sufficiently spread, either locally, lymph nodes, or even metastases.

This result is by previous findings. A Dutch study that collected data on penile cancer patients over 17 years found a similar, albeit slightly lower, proportion of staging distribution than in this study. However, this study also found a lower proportion of metastatic findings at diagnosis of penile cancer, which was 29%.[14] Another study in Denmark, collecting data on penile cancer for 30 years, found similar results. In addition, this study also found that the proportion of cancer staging at diagnosis did not change over the 30 years of the study.[15]

Meanwhile, the grading characteristics found in this study were dominated by grade II (46.3%), with histopathological characteristics dominated by usual squamous cell carcinoma (91.2%). These histopathological characteristics are consistent with previous studies in Chinese.[16] The proportion of grading distribution found is different from that found in other studies. Research in China found that around 60% of penile cancer patients with well-differentiated or grade I grades.[16,17]. However, the findings of the proportion of tumor grades in this study are by studies in the Netherlands which found around 35% with grade II.[14]

The descriptive survival analysis found that 47 (58.8%) subjects were still alive as of February 2022, while the remaining 33 (41.2%) had died. The mean length of survival obtained from the Kaplan-Meier descriptive analysis was 60.65 (95% CI 51.25 – 70.04) months. 2-year survival in subjects was found to be 51%. These survival rates are lower than those found in general Dutch and European studies.[14,18] One of the potential causes of this difference is the difference in the quality of care and adherence to treatment in the study's target population.

The main analysis of this study, using the Cox regression test with time dependency adjustment for confounding variables of a combination of operative therapy and chemotherapy, identified two independent variables as survival predictors, namely, stage N and cancer cell subtype. Patients with stage N3 were found to have an increased risk of mortality with HR 3.55 (95% CI 1.03 – 12.31) compared to patients with stage N0. Meanwhile, patients with condylomatous penile cancer had an increased mortality risk with HR 6.77 (95% CI 1.02 – 44.85) compared to patients with usual SCC penile cancer.

The role of high N staging as a predictor of mortality has been recognized previously. A study in the Netherlands found an increased mortality risk for patients with penile cancer with stages N1-3 compared to patients with stage N0, with an HR of 3.0 (95% CI 2.3 – 3.8).[14] Similar findings were also found in other studies. Li et al. (2015) even found an association with an increased risk of higher mortality and increased N staging in patients with penile cancer.[19]

Even so, the findings of this study are slightly different compared to the two previous studies. Although identifying the role of staging N as a predictor of mortality, this study identified N3 specifically as a predictor of mortality, but not N1 and N2. This difference can be explained by the sample size and the number of samples in each stage N. Table 2 shows that only 12 (15%) of the samples fall into category N1, and 16 (20%) fall into category N2. As is known about statistical analysis, the small sample size can reduce the precision of statistical estimates, resulting in estimates with wide confidence intervals.[20]

The other findings regarding the role of the condylomatous penile cancer subtype as a predictor of mortality are different from previous findings. Several previous studies have reported the relationship between penile cancer subtypes and mortality risk, but there is controversy about which subtype predicts mortality. One study reported the verrucous subtype as a predictor of mortality compared to the usual SCC subtype.[16] Meanwhile, other studies reported differences in mortality risk between penile cancer subtypes of SCC and non-SCC, where non-SCC subtypes were associated with an increased risk of mortality.[21] Despite this controversy, existing studies have shown the usual SCC subtype to have a lower mortality risk than the other subtypes.

The variation in findings regarding the relationship between subtypes and the risk of mortality in penile cancer patients may also be due to the small number of cases of penile cancer with subtypes other than usual SCC. One large study that analyzed data from several healthcare centres over 50 years found that less than 10% of penile cancer patients were diagnosed with subtypes other than usual SCC.[9] Similar proportions were found in two studies that found the cancer subtype to predict mortality.[16,21] Rare cases of penile cancer other than the usual subtype of SCC cause the resulting estimate to be less accurate. More studies with larger sample sizes are needed to reach an academic consensus on the role of subtypes in the mortality prognosis of penile cancer.

In multivariate analysis, several predictive factors analyzed as independent variables in this study were found not to be significantly associated with mortality risk. These factors include T staging, grading, LVI, and NLR. The relationship between T staging as a predictor of mortality is associated with tumor localization, so its role can be said to be closely related to N staging, which is known to be the main predictor of mortality in penile cancer.[9,12,22] The role of NLR as a predictor of mortality needs to be better defined. Previous studies argued that the potential of NLR as a predictor of mortality was due to its association with lymph node spread (stage N), making NLR an indirect predictor. However, this association must be stronger in multivariate tests.[13] The same explanation can also be put forward for LVI. Although found to be a predictor of mortality and decreased 3-year survival, this association was suspected based on the relationship between LVI and N staging, which are known to be one of the strongest predictors of mortality in penile cancer.[12] The relationship between tumor grade as a predictor of mortality in penile cancer is based on the research of Aita et al. (2016). This study specifically studied grade as a predictor of mortality for patients without lymph node spread (stage N0). The analysis in this study involving stage N as an independent variable could explain the absence of a significant role for increased T stage, grading, NLR, and LVI as predictors of mortality. In contrast, the results of our analysis confirmed N staging as a major predictor of mortality in penile cancer.

In this study, several variables were included and controlled by analysis. The variable combination of neo-adjuvant chemotherapy and adjuvant TIP regimen received by penile cancer patients was significantly related to survival in the Kaplan Meier bivariate test with a median survival of 51.51 months (95% CI 32.12-70.90) with a p-value <0.05. This is comparable to a study conducted by Xu et al. (2019) which found that in a median follow-up of 39.6 months, there was an increase in the median overall survival (OS) for 23 months (95% CI 6.122-39.898, p< 0.001) which is statistically significant. Inguinal KGB dissection is also one of the therapies given to penile cancer patients.[23] In this study, it was found that patients who received inguinal lymph node dissection had a better average length of survival compared to those who did not have lymph node dissection (60.49 months (95% CI 51.14-69.83)) but not statistically significant (p = 0.054). This is different from the study by Hu et al. (2020), it was found that inguinal lymph node dissection was a significant predictive factor for specific survival of penile cancer with an HR of 0.32 (95% CI (0.17 - 0.60, p<0.001).[24] This was related to the status of lymph nodes in penile cancer, which is a significant predictor of survival, so inguinal lymph node dissection, which is local control and chemotherapy as a systemic control, can increase the duration of survival of penile cancer patients.[23,25,26]

In addition, this study also found that patients who received total penectomy surgery had a longer average survival compared to those who underwent partial penectomy or did not have surgery, but this result was not statistically significant. This is different from a study conducted by Kamel et al. (2018) which found that patients with partial penectomy had better 3-year survival compared to total penectomy (83% vs 76% respectively), with HR 0.82 (CI95% 0, 64-1.04) but not statistically significant. Both types of surgery are more aimed at removing the primary tumor and controlling the recurrence of the primary tumor, so they do not play a significant role as predictors of survival.[27]

The findings in this study indicate that the risk factors for mortality are comparable to reports from previous studies. Some of the differences found can be explained by differences in the characteristics of penile cancer patients found in Bali or by the lack of accuracy of statistical estimates related to the sample size involved.

The advantage of this study is that it is one of the first to report longitudinal survival of penile cancer patients in Indonesia. However, as mentioned above, this study needs to improve regarding the sample size included in the analysis. The implication of the weakness of this study is the need for further research involving more healthcare facilities. The fact that penile cancer is a rare disease. (Montes Cardona & García-Perdomo, 2017) indicates the need for a multicenter collaborative study to obtain a representative sample size to describe penile cancer in Indonesia. This representative data is important to see whether the clinical characteristics and survival of penile cancer patients in Indonesia are comparable to other data worldwide.

CONCLUSION

This study showed that penile cancer lymph node status (N) affected the survival of penile cancer patients, where patients with stage N3 were found to have HR 3.55 (95% CI 1.03 – 12.31). Cell subtype also affects the survival of penile cancer patients where patients with condylomatous penile cancer subtype are found with HR 6.77 (95% CI 1.02 – 44.85).

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CONFLICT OF INTEREST
The authors have no conflict of interest related to the study, authorship, and/or article publication to declare.

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