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Relationship of Stromal Tumor Infiltrating Lymphocytes (STILs) with Histopathology Grading in Penile Squamous Cell Carcinoma

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ABSTRACT

Background
Penile squamous cell carcinoma is the most common penile malignancy found in the world. Assessment of stromal tumor-infiltrating lymphocytes (STILs) associated with grading against penile squamous cell carcinoma can provide a potential prognostic feature and determine the treatment.

Method
Cross-sectional analytical study with 32 samples of histopathological preparations diagnosed as penile squamous cell carcinoma at H. Adam Malik Hospital Medan. The assessment of stromal TILs was carried out by assessing the number of lymphocyte inflammatory cells in the peritumoral stroma and then determined the assessment score, zero score no lymphocytes (minimum), score one found 0-10% lymphocytes (moderate), score two found 20-40% lymphocytes (massive), score three found 50-90% lymphocytes. Grading assessments are categorized into grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated).

Result
The most grading found was grade II (43.8%) and the most STILs found were score three (50.0%). There is a significant relationship between grading and STILs in penile squamous cell carcinoma (p value=0.0001) i.e. the higher the STILs score, the lower the tumor grade.

Conclusion
There is a relationship between STILs and histopathological grading in Penile Squamous Cell Carcinoma therefor it can be used as a prognosis indication in patients with penile squamous cell carcinoma.

Keywords: Penile squamous cell carcinoma, Tumor Infiltrating Lymphocytes, grading.

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INTRODUCTION

Penile carcinoma is one of the rare malignancies.[1-5] The majority of malignant tumors in the penis are squamous cell carcinoma.[1,2] Based on GLOBOCAN Data, International Agency for Research on Cancer (IARC), it is known that 2020 there were 36,068 new cases and 13,211 deaths from penis carcinoma worldwide in 2020.[2,3] The incidence of penile carcinoma, is more prevalent in older ages, and is increasing at ages over 80 years.[6] In Indonesia, penile carcinoma ranks 29th. The incidence rate of new cases was 1,017 cases (0.26%) and 347 (0.15%) deaths, the incidence rate of new cases <5 years was 2,954 (2.14%).[7] Pathogenesis of squamous cell carcinoma of the penis is thought to be caused by poor personal hygiene, not performing circumcision, HPV virus infection (Human Papilloma Virus), chronic inflammation of the skin of the penis, is the most frequent risk factor in penile squamous cell carcinoma.[1-3,10,11]

The tumor histology grade is important in the prediction factor against the involvement of the lymph node which is an important factor in determining the outcome of penile squamous cell carcinoma.[8,37] Assessment of Tumor Infiltrating Lymphocytes has been realized by pathologists to have an important role in determining prognosis and predictions of the potential significance of many tumors, and also as clinical and research immunotherapy.[37] Researchers are interested in doing this research because it has never been done before.

METHODS

This research is an analytical study with a cross-sectional approach. The research was conducted at the PA DEPARTMENT OF FK USU from January 2022 to August 2022. The population of this study was all secondary data and paraffin blocks as well as microscopic slides from patients diagnosed with penile squamous cell carcinoma with Hematoxylin & Eosin staining that met the inclusion and exclusion criteria in the Department of Anatomic Pathology Faculty of Medicine, University of North Sumatra and Anatomic Pathology Unit of RSUP Haji Adam Malik Medan. This sample size was taken based on the proportion estimation formula and obtained 32 samples. The variables in this study were sTILs (stromal tumor-infiltrating lymphocytes) as independent variables and penile squamous cell carcinoma as dependent variables. The histopathological grade of penile squamous cell carcinoma is assessed based on a grade grading system according to WHO and ISUP, which is assessed based on core pleomorphism with varying amounts of keratin production, which is divided into 3 (three) namely: Grade I is well-differentiated carcinoma, where shows the cytology of a normal squamous network. A network architecture with a dominant pattern of sheets and an irregular nest pattern accompanied by minimal reactive stroma. Grade II is moderately differentiated carcinoma, whereby t cells form irregular, smaller nesting patterns and reactive stroma. Grade III is poorly differentiated carcinoma, which is difficult to find keratin pearls with irregular and polymorphic tumor cell growth patterns. Mitosis is commonly encountered. Stromal Tumor Infiltrating Lymphocytes (STILs) are lymphocyte inflammatory cells that migrate to the vicinity of the tumor, which is an antitumor immune response and is a key mechanism for controlling tumor progressiveness. In this study, the STILs that were calculated were lymphocyte cells. The scoring system used to calculate the number of STILs is 0=no lymphocytes, 1=minimal lymphocytes found, namely 0-10% stromal TILs, 2=moderately lymphocytes i.e. 20-40% stromal TILs, 3=massive lymphocytes, namely 50-90% stromal TILs.[37] The collected data will be analyzed using the statistical program SPSS v 20. Univariate analysis is performed to obtain the mean, standard deviation, median, minimum value, and maximum value. All data were first tested for normality with the Shapiro-Wilk test, where the $p>0.05$ value stated that the data had a normal distribution.

Bivariate analysis was performed to analyze the relationship of TILs with histopathological grading of squamous cell carcinoma in the penis with the Chi-Square Countigency Table test where $p<0.05$ values were statistically significant.

RESULT

From 40 samples with penectomy in this study diagnosed with penile squamous cell carcinoma from 2017 to 2021 at Haji A. Malik Hospital Medan, only 32 samples had complete medical record data.

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Table 1. Characteristics of penile squamous cell carcinoma based on age.

Age characteristics	frequency (n=32)	Percentage (%)
<31 years old	0	0.0
30-39 years old	5	15.6
40-49 years old	11	34.4
50-59 years old	6	18.8
≥ 60 years old	10	31.3
Total	32	100.0

The percentage of people with penis SCC is highest at the age of 40-49 years old, which is 34.4%. The average age of people with penile squamous cell carcinoma is 51.62 years with the youngest age, being 31 years old and the oldest age is 83 years old. The second most age group is ≥60 years old, namely 31.3%, the age group 50-59 years old 18.8%, and the age group 30-39 years old 15.6%.

Table 2. Characteristics of penile squamous cell carcinoma based on tumor location

Tumor location	Frequency (n=32)	Percentage (%)
Glans	21	66.1
Preputium	0	0.0
Coronal sulcus	0	0.0
Corpus penis	0	0.0
More than one location	4	12.1
No data	7	21.8
Total	32	100.0

The location of the most penile tumors is the glans, which is 66.1%, while in prepuce, coronal sulcus and penile corpus 0%.

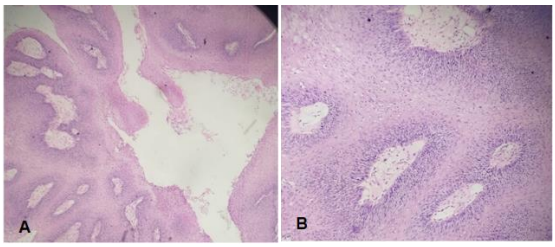

Figure 1. A. Warty carcinoma with 40 times magnification, H&E.

Table 3. Characteristics of penile squamous cell carcinoma based on histopathological diagnosis

Clinical diagnosis	Frequency (n=32)	Percentage (%)
Keratinizing SCC	27	84.4
Non-keratinizing SCC	5	15.6
Total	32	100.0

The characteristics of the research sample based on clinical diagnosis were found in the penis SCC keratinizing diagnosis group, which was 84.4% and the non-keratinizing SCC diagnosis group was 15.6%.

In this study, the distribution of squamous cells of the penis stromal tumor-infiltrating lymphocytes (sTILs) was also carried out. In determining the assessment, a score was divided into 4, namely scores of 0,1,2 and 3, where a score of 0 did not have a lymphocyte per field of view, score 1 was found 0-10% lymphocytes per field of view, score 2 was found 20-40% lymphocytes per field of view, and score 3 was found lymphocytes as much as 50-90% per field of view. [37]

Table 4. Distribution of penile squamous cell carcinoma based on stromal tumor infiltrating lymphocytes (sTILs).

Stromal tumor infiltrating lymphocytes	Frequency (n=32)	Percentage (%)
Shoes 0	0	0.0
Shoes 1	5	15.6
Shoes 2	11	34.4
Shoes 3	16	50.0
Total	32	100.0

Based on the table above, it was found that the highest assessment of stromal tumor-infiltrating lymphocytes was rank 3, namely a massive lymphocyte, which was 50.0%, then the second rank namely a moderate lymphocyte which was 34.4% while for rank 3, namely a minimum lymphocyte of 15.6%

Table 5. Characteristics of penile squamous cell carcinoma based on grading.

Grading	frequency (n=32)	Percentage (%)
Grade I	9	28.1
Grade II	14	43.8
Grade III	9	28.1
Total	32	100.0

The highest grading percentage is grade II, which is 43.8%, while in grade I and grade III, it is 28.1%.

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Table 6. The Association between grading and stromal tumor-infiltrating lymphocytes in penile squamous cell carcinoma.

Variable	Grade I	Grade II	Grade III	Total	value	p*
	f (%)	f (%)	f (%)	f (%)		
Skor TILs						
1	0 (0.0)	1 (3.1)	4 (12.5)	5 (15.6)	<0.527	0.0001
2	2 (6.3)	5 (15.6)	4 (12.5)	11 (34.4)		
3	7 (21.9)	8 (25.0)	1 (3.1)	16 (50.0)		
Total	9 (28.1)	14 (43.8)	9 (28.1)	32 (100.0)		

*) Somers'd correlation test

From the results of the Somers'd correlation test, the relationship value between grading and stromal tumor-infiltrating lymphocytes was obtained that there were no patients with sTILs score 1 with grade I (0.0%), sTILs score 2 with grade I 6.3%, sTILs score 3 with grade I 21.9%, sTILs score 1 with grade II 3.1%, sTILs score 2 with grade II 15.6%, sTILs score 3 with grade II 25.0%, sTILs score 1 with grade III 12.5%, sTILs score 2 with grade III 12.5%, sTILs score 3 with grade III 3.1%.

DISCUSSION

The results of the study showed that 32 samples diagnosed with penile squamous cell carcinoma averaged 51.62 years old. This is in accordance with research conducted by Douglawi et al in 2017 where penile squamous cell carcinoma is a male malignancy that rarely and always occurs at the age of 50-70 years old. [2] The same explanation was also stated in research by Mahatma G et al in 2019 and Marchionne et al in 2017 that the average age of people with squamous penis cell carcinoma is 50-70 years old.[3.12] The most locations of penile squamous carcinoma in this study were in the glans region of the penis, which was 21 case is in line with the results of a study by Marchionne et al in 2017, namely the most common lesions of penile squamous cell carcinoma found in glans as much as 48%.[12]

For grading characteristics, this study revealed the most common grade found grade II, which is 43.8%. Then followed by grading I and II as much as 28.1%. This is in line with the research of Laksmi et al in 2022 which found the most cases with grade II, namely 54.5%. [62] Zheng et al in 2020 reported that cases with grade II were found as many as 57.3%. [63] Digambiro in 2014 found that grading II and III were the most cases encountered at 33.3%. Sali et al in 2019 said that 59% of cases were grade II. [5] Grade tumors can predict metastases to lymph nodes and have a relationship with survival rates. Most tumor cells of small nest forms in the presence of reactive stroma are moderately differentiated carcinoma (grade II).[62]

In this study, it was found that the largest stromal tumor infiltrating lymphocytes score was a score of 3 in the presence of massive lymphocytes, namely in grade II penile squamous cell carcinoma. It can be seen that the role of tumor-infiltrating lymphocytes is a factor in the body's defense against tumor attacks. Lymphocyte infiltration is associated with a good clinical picture especially in rapidly proliferating tumors.[41] TILs are defined as lymphocytes that are located in the tumor and or surround the tumor where these include CD8+, CD4+, CD45+ and CD20+, NK cells, and so on.[42] This study only assessed sTILs and did not assess iTILs. This study is expected to provide a prognostic feature of cases especially lower grades. According to Jiang D et al in 2017 it was said that the presence of sTILs has a better and stronger prognostic impact when compared to iTILs.[66] According to Almangush et al in 2022, said that the estimation of TILs examination can be seen by routine H&E staining and can determine the prognostics of the sufferer.[67] According to Li J et al, the presence of TILs in the tumor environment indicates the ongoing reaction of the body's immunity against the tumor reaction so that a better state of the sufferer is achieved.[64] IL can express activation markers and release vascular endothelial growth factor (VEGF) and basic growth factors that can trigger lymphangiogenesis and angiogenesis so that cancer cells can spread through lymphatic circulation to lymph nodes (KGB).[41] Most of the effector cells that play a role in antitumor mechanisms are CD8+ T lymphocytes, which play a role in killing virus-infected cells or allogeneic cells. CD4+ T lymphocytes act as antitumors by producing various cytokines that are lubricated by Tc lymphocytes.[41]

In this study, statistical test results obtained p-value value <0.5 showed a strong

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relationship (p-value=0.0001), therefore it can be concluded that there is a significant relationship between histological grading and stromal infiltrating lymphocyte tumors in penile squamous cell carcinoma. In this case, the number of stromal tumor-infiltrating lymphocytes is higher at grade II compared to higher grading. The test results obtained a sufficient correlation (0.41-0.60) and a negative correlation (the higher the TILs score, the lower the grade tumor, and vice versa). The results obtained in this study are expected to help provide a prognostic indicator in penile squamous cell carcinoma. Further research requires a further understanding of the role of TILs on penile squamous cell carcinoma against histopathological grading by assessing the histopathological subtypes of HPV-related tumors and HPV non-related tumors.

CONCLUSION

The highest number cases with penile squamous cell carcinoma is at the age of 40-49 years, with the average age being 51.62 years old. The youngest age is 31 years old and the oldest age is 83 years old. The location of the most tumors is in the glans penis. The most clinical diagnosis is keratinizing squamous cell carcinoma of the penile. The most tumor locations are in the glans region of the penis as much as 66.1%. The most common clinical diagnosis is keratinizing SCC of the penis. The highest number of stromal tumor-infiltrating lymphocytes is a score of 3, which is a massive lymphocyte. There is a relationship between sTILs and histopathological grading, which is in grade II and has a significant correlation.

REFERENCES

1. Cubilla AL, Amin MB, Ayala A, Ayala G, Chaux A, Corbishley C, et al. Malignant epithelial tumours. Moch H, Hunphrey PA, Ulbright TM, Reuter VE, editors. In World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs. IARC Lyon. 2016. 262-286.
2. Douglawi A, Masterson TA. Updates on the epidemiology and risk factors for penile cancer. 2017. Available from: file:///C:/Users/User/Documents/Jurnal_proposal_magister/douglawi2017.pdf
3. Mahatma G, Wahid I. Penile squamous cell carcinoma. 2019. Available from: file:///C:/Users/User/Downloads/646-1651-1-PB%20(1).pdf
4. Ferrandiz-Pulido C, de Torres I, Garcia-Patos V. Penile squamous cell carcinoma. [cited 2012 aug 5]. Available from: file:///C:/Users/User/Documents/Jurnal_proposal_magister/penile%20squamous%20cell%20carcinoma.pdf
5. Sali AP, Menon S, Murthy V, Prakash G, Bakshi G, Joshi A, Desai SB. A modified histopathologic staging in penile squamous cell carcinoma predicts nodal metastasis and outcome better than the current AJCC staging. 2020. Available from: https://sci-hub.se/https://doi.org/10.1097/pas.0000000000001490
6. Digambiro RA, Alferally I, Delyuzar. The relationship between the degree of histopathology of penile carcinoma and the immunohistochemistry display of HER-2. Pathology magazine. 2016. Available from: file:///C:/Users/User/Downloads/204-Article%20Text-358-1-10-20171212.pdf
7. International agency for Research on Cancer. Indonesia. Source: GLOBOCAN 2020. Available from:
8. Aydin AM, Hall M, Bunch BL, Branthoover H, Sannasardo Z, Mackay A, et al. Expansion of tumor-infiltrating lymphocytes (TIL) from penile cancer patients. Elsevier. 2021. In: https://doi.org/10.1016/j.intimp.2021.107481
9. Dillner J, Krogh GV, Horenblas S, Meijer C. Etiology of Squamous cell carcinoma of the penis. 2000. Available in: https://sci-hub.se/https://doi.org/10.1080/00365590050509913
10. Madsen BS, van den Brule A, Jensen HL, Wohlfahrt J, Frisch M. Risk factors for squamous cell carcinoma of the penis-population-based case-control study in Denmark. 2008. In: https://sci-hub.se/https://doi.org/10.1158/1055-9965.epi-08-0456
11. Sonpavde G, Pagliaro LC, Buonerba, Dorff TB, Lee RJ, Lorenzo GD. Penile cancer: current therapy and future directions. 2013. In: https://sci-hub.se/https://dx.doi.org/10.1093%2Fannonc%2Fmds635
12. Marchionne E, Hui A, Perez C, Khachemoune A. Penile squamous cell carcinoma: a review of the literature and case report treated with Mohs micrographic surgery.2017. In: https://sci-hub.se/https://dx.doi.org/10.1590%2Fabd1806-4841.20175009
13. Lohneis P, Boral S, Kaufmann AM, Lehmann A, Schewe C, Dietel M, et al.

Maj Patol Indones 2024; 33(2): 766-773
DOI: 10.55816/mpi.v33i2.580

P-ISSN 0215-7284
e-ISSN 25279106
Accredited by KEMENRISTEKDIKTI/Sinta-3

Human papilloma virus status of penile squamous cell carcinoma is associated with differences in tumor-infiltrating T lymphocytes. 2015. In: https://sci-hub.se/https://doi.org/10.1007/s00428-014-1713-4
14. International Agency for Research on Cancer. Indonesia. Source: Globocan 2021. Available from: https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf
15. Mescher AL. Junqueira's Basic Histology Text & Atlas. 15th edition. Lange. 2018. 21; 456-458.
16. Sontakke YA. Textbook of Human Histology. CBS publisher % distributors. 1st e-book edition. 2020. 22;264-265.
17. Ficcarra V, Akduman B, Bouchot O, Palou J, Tobias-Machado M. Prognostic factors in penile cancers. 2010. Available in: https://sci-hub.se/https://doi.org/10.1016/j.urology.2010.04.008
18. Prayoga DA, Tranggono U. Clinical evaluation and management of penile cancer at Sardjito hospital, Yogyakarta. Indonesian journal of cancer. 2016;10 (1):29-34:doi:10.33371/ijoc.v10i1.411
19. Boskey E. The anatomy of the penis. Oktober 2021. Available from: https://www.verywellhealth.com/penis-anatomy-4777189
20. Hsu GL, Hsieh CH, Wen HS, Hsu WL, Wu CH, Fong TH, et al. Anatomy of the human penis: The relationship of the architecture between skeletal and smooth muscle. 2004. Available from: https://sci-hub.se/https://doi.org/10.1002/j.1939-4640.2004.tb02810.x
21. Mohan H. Textbook of pathology. Seventh edition. India. 2015. 21: 702-703
22. Rubin MA, Kleter B, Zhou M, Ayala G, Cubilla AL, Quint W,et al. Detection and typing of human papilloma virus DNA in penile carcinoma. 2001. Available from: https://sci-hub.se/https://doi.org/10.1016/s0002-9440(10)62506-0
23. Heideman DAM, Waterboer T, Pawlita M, Diemen P, Nindl I, Leijte JA, et al. Human papilloma virus 16 is the predominant type etiologically involved in penile squamous cell carcinoma. 2007. Available from: https://sci-hub.se/https://doi.org/10.1200/jco.2007.12.3182
24. Ottenhof SR, Bleeker MCG, Heideman DAM, Snijders PJF, Horenblas S. Etiology of penile cancers. Muneer A, Horenblas S editors. In: Textbook in penile cancer. Springer. 2017. 2: 22-26
25. Miralles-Guri C, Bruni L, Cubilla AL, Castellsague X, Bosch FX, Sanjose SD. Human papilloma virus prevalence and type distribution in penile carcinoma. 2009. Available from: https://sci-hub.se/https://doi.org/10.1136/jcp.2008.063149
26. Renaud-Vilmer C, Cavelier-Balloy B, Verola O, Morel P, Servant JM, Desgrandchamps F, et al. Analysis of alterations adjacent to invasive squamous cell carcinoma of the penis and their relationship with associated carcinoma. Available from: https://sci-hub.se/https://doi.org/10.1016/j.jaad.2009.06.087
27. Djajadiningrat RS, Jordanova ES, Kroon BK, Werkhoven EV, de jong J, Pronk DTM, Snijders PJF, et al. Human papilloma virus prevalence in invasive penile cancer and association with clinicical outcome. 2015. Available from: https://sci-hub.se/https://doi.org/10.1016/j.juro.2014.08.087
28. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Penile cancer: importance of circumcicion, human papilloma virus and smoking in situ and invasivve disease. 2005. Available from: https://doi.org/10.1002/ijc.21009
29. Tseng HF, Morgenstern H, Mack T, Peters RK. Risk factors for penile cancer: result of population-based case-control study in Los Angeles County (United States). 2001. Available from: https://sci-hub.se/https://doi.org/10.1023/a:1011266405062
30. Hernandez BY, Wilkens LR, McDuffie K, Zhu X, Thompson P, Shvetsov YB, et al. Circumcicion and human papilloma virus infection in men: a site specifix comparison. 2008. Available from: https://sci-hub.se/https://doi.org/10.1086/528379
31. Abdulla A, Daya D, Pinthus J, Davies T. Buried penis: an unrecognized risk factor in the development of invasive penile cancer. 2012. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3478392/
32. Konan PG, Vodi CC, Dekou AH, Fovana A, Gowe EE, Manzan K. Cancer of the penis associated with HIV: a report of three cases presenting at the CHU cocody, ivory coast. 2015. Available from:

P-ISSN 0215-7284
e-ISSN 25279106
Accredited by KEMENRISTEKDIKTI/Sinta-3

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4647508/
33. Singh AK, Saokar A, Hahn PF, Harisinghani MG. Imaging of penile neoplasms. 2005. Available from: https://sci-hub.se/https://doi.org/10.1148/rg.256055069
34. Korzeniowski MA, Crook JM. Contemporary role of radiotherapy in the management of penile cancer. 2017. Available from: https://sci-hub.se/https://doi.org/10.21037/tau.2017.07.02
35. Chu C, Yao K, Lu J, Zhang Y, Chen K, Lu J, et al. Immunophenotypes based on the immune microenvirontment allow for unsupervised penile cancer patient stratification. 2020. Available from: https://sci-hub.se/https://doi.org/10.3390/cancers12071796
36. Ottenhof SR, Djajadiningrat RS, Thygesen HH, Jakobs PJ, Jozwiak K, Heeren AM, de Jong J, et al. The prognostic value of immune factors in the tumor microenvirontment of penile squamous cell carcinoma. 2018. Available from: https://sci-hub.se/https://doi.org/10.3389/fimmu.2018.01253
37. Hendry S, Salgado R, Gevaert T, Russell PA, John T, Thapa B, et al. Assessing tumor-infiltrating lymphocytes in solid tumors: a practical review for pathologist and proposal for a standardized method from the international immune-oncology biomarkers working group: part 2: TILs in Melanoma, Gastro intestinal tract carcinomas, non-small cell lung carcinoma and mesothelioma, endometrial and ovarian carcinomas, squamous cell carcinoma of the head and neck, genitourinary carcinoma, and primary brain tumors. 2017. Available from: file:///C:/Users/User/Downloads/TWORKING%20TILS2%20(1).pdf
38. Erbersdobler A. Pathology and histopathological evaluation of penile cancer. Urologe. 2018; 57:391-397
39. Pullen RL. Penile cancer. Nursing. Wolters kluwer health. 2018; 48(4):32-39. Available from: https://sci-hub.se/10.1097/01.NURSE.0000531005.17471.7d
40. Morris BJ, Krieger JN. Penile inflammatory skin disorders and the preventive role of circumsision. Int J Prev Med. 2017; 8-32.
41. Diana D, Kusmardi. Tumor infiltrating lymphocutes and their role in breast carcinoma. Indonesian Pathology Magazine. 2020; 29(1): 30-40.
42. Winarti NW, Arijana IGKN, Tunas IK, Widyadharma IPE. Tumor infiltrating lymphocytes and expression of granzyme B in penile squamous cell carcinoma at Sanglah General Hospital, Bali. 2020. Available from:DOI:10.5455/IJMRCR.
43. Ahn SG, Jeong J, Hong SW, Jung WH. Current issues and clinical evidence in tumor-infiltrating lymphocytes in breast cancer. Journal of pathology and translational medicine. 2015; 49(5):355-363.DOI:https://doi.org/10.4132/jptm.2015.07.29
44. Abbas AK, Lichtman AH, Pillai S. Cellular and molecular immunology. 7th ed. Philadelphia. Saunders Elsevier. 2012;13:389-406.
45. Sasada T, Suekane S. Variation of tumor infiltrating lymphocytes in human cancers: Controversy on clinical significance. Immunother. 2011;3:1-24
46. Engelsgjerd JS, LaGrange CA. Penile cancer. Statpearls Publishing LLC. 2020.
47. Micali G, Nasca MR, Innocenzi D, Schwartz RA. Penile cancer. American Academy of Dermatology. 2006.p. 369-391. Available from:DOI:10.1016/j.jaad.2005.05.007
48. Parker DC. Malignant dermatological disease of the male genitalia. Medscape. 2017. Available from: http://emedicine.medsape.com/article/454810-overview
49. Joshi SS, Handorf E, Strauss D, Correa AF, Kutikov A, Chen DYT, et al. Treatment Trends and Outcomes for Patients with Lymph Node-Positive Cancer of The Penis. JAMA oncol. 2018;4(5):643-649
50. Suh CH, Baheti AD, Tirumani SH, Rosenthal MH, Kim KW, Ramaiya MH, Shinagare AB. Multimodality imaging of penile cancer:what radiologists need to know. Springer science+Business Media Network. 2015;40:424-435. Available from:DOI:10.1007/s00261-014-0218-6.
51. Vries HM, Brouwer OR, Heijmink S, Horenblas S, Vegt E. Recent developments in penile cancer imaging. Walters Kluwer Health. 2018. Available from: https://sci-hub.se/https://doi.org/10.1097/mou.0000000000000585
52. Krishna S, Shanbhogue K, Schieda N, Morbeck F, Hadas B, Kulkarni G, et al. Role of MRI in staging of Penile Cancer.

P-ISSN 0215-7284
e-ISSN 25279106
Accredited by KEMENRISTEKDIKTI/Sinta-3

CME article. 2020. Available from: DOI:10.1002/jmri.27060
53. Chaux A, Cubilla AL. The role of Human papillomavirus infection in the pathogenesis of penile squamous cell carcinomas. 2012. Available from: DOI: 2011.09.001
54. Cubilla AL, Epstein J. The world health organization 2016 classification of penile carcinomas: A review and update from the international society of urological pathology
55. Kreike B, Van Kouwenhove M, Horlings H, Weigelt B, Peterse H, Bartelink H, van de Vijver MJ. Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas. 2007. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2242660/
56. Cubilla AL, Velazquez EF, Amin MB, Epstein J, Berney DM, Corbishley CM. The World Health Organization 2016 Classification of Penile Carcinomas: a review and update from the International Society of Urological Pathology expert driven recommendations. 2018. Available from: https://sci-hub.se/https://doi.org/10.1111/his.13429
57. Revelations USA. Medical Statistics. 2002.
58. Spiess PE, Dhillon J, Baumgarten AS, Johnstone PA, Giuliano AR. Pathophysiological Basis of Human Papillomavirus in Penile Cancer: Key to Prevention and Delivery of More Effective Therapies. CA Cancer J Clin. 2006. Available from: doi: 10.3322/caac.21354.
59. Lorga L, Marcu RD, Diaconu CC, Stanescu AMA, Stoian AP, Mischianu DLD, et al. Penile carcinoma and HPV infection (Review). 2020; 20(1):91-91. Available from: https://doi.org/10.3892%2Fetm.2019.8181
60. Kidd LC, Chaing S, Chipollini J, Giuliano AR, Spiess PE, Sharma P. Relationships beetwen human papillomavirus and penile cancer implications for prevention and treatment. 2017. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5673821/pdf/tau-06-05-791.pdf
61. Dorofte L, Grelaud D, Fiorentino M, Giunchi F, Ricci C, Franceschini T, et al. Low level of interobserver concordance in assessing histological subtype and tumor grade in patients with penile cancer may impair patient care.
62. Laksmi LI, Seja IA, Warli SM. The association between tumor budding peritumoral and histologic grade in penile squamous cell carcinoma. 2022. Available from: http://dx.doi.org/10.3889/oamjms.2022.8592
63. Zheng W, Li K, Zhu W, Ding Y, Wu Q, Tang Q, et al. Normogram prediction of overall survival based on log odds of positive lymph nodes for patient with penile squamous cell carcinoma. 2020;9:5425-5435.
64. Li J, Tang Y, Huang L, Yu Q, Hu G, Zou Y, et al. A high number of stromal tumor-infiltrating lymphocytes is a favorable independent prognostic factor in M0 (stages I-III) esophageal squamous cell carcinoma.
65. Li K, Le X, Wang J, Fan C, Sun J. Tumor location may independently predict survival in patients with M0 squamous cell carcinoma of the penis. Front oncol, 2022; 12: 927088. Available from: https://doi.org/10.3389%2Ffonc.2022.927088
66. Jiang D, Liu Y, Wang H, Song Q, Sujie A, Huang J, et al. Tumour infiltrating lymphocytes correlate with improved survival in patients with oesophageal squamous cell carcinoma. Scientific reports. 2017; available from:https://www.nature.com/articles/srep44823.pdf
67. Almangush A, Jouhi L, Haglund C, Makitie A, Hagstrom J, Leivo I. Tumour infiltrating lymphocytes in oropharyngeal cancer: a validation study according to the criteria of the International immune-oncology buiomarker working group. British journal of cancer. 2022. Available from:file:///C:/Users/User/Downloads/Tumour-infiltrating_lymphocytes_in_oropharyngeal_c.pdf