

Histological grade¹⁻⁶ (Required)

Reason/Evidentiary Support

Accurate staging and grading of tumours are used to determine subsequent clinical management and follow-up. Different subtypes of penile carcinoma have been defined, which appear to be associated with different outcomes and may also therefore justify the adoption of different treatment strategies.

There is no consensus concerning grading, and the most recent World Health Organisation (WHO) classification (2016)¹ recommends a three step grading system based on degree of pleomorphism and keratinisation with the overall grade determined by the worst area no matter how small the percentage of the tumour. The most recent College of American Pathologists (CAP) guidelines⁷ offer some outline global guidance which is applicable to usual type squamous carcinomas.

The “classical” method defines well-, moderately-well and poorly-differentiated carcinomas on the basis of the degree of cytological atypia, keratinisation, intercellular bridges and mitotic activity (see Table 1). These criteria are difficult to apply to some subtypes of penile carcinoma, for example verrucous carcinomas which are well differentiated but often show little or no keratinisation. Sarcomatoid change is a separate category, which is often combined with other tumour types and which conveys a very poor prognosis. All tumours with sarcomatoid areas should be graded as Grade 3 but this finding also needs to be noted separately as tumours with sarcomatoid areas have a worse prognosis than Grade 3 tumours generally.⁸

Tumours are generally graded on their worst component. Although at one time a threshold of 50% of poorly-differentiated cancer was suggested as the cut-off point most predictive of nodal metastases, it has recently been shown that any component of high-grade tumour conveys a worse prognosis so should be included in the final grade.⁶ Every effort should be made to assign a final grade as this is an important prognostic factor and this grade must be based on the most poorly-differentiated component, no matter how small.

Table 1: Grading of penile squamous cell carcinoma*

Feature	Grade 1	Grade 2	Grade 3	Sarcomatoid areas present (Grade 3)
Cytological atypia	Mild	Moderate	Anaplasia	Sarcomatoid
Keratinisation	Usually abundant	Less prominent	May be present	Absent
Intercellular bridges	Prominent	Occasional	Few	Absent
Mitotic activity	Rare	Increased	Abundant	Abundant
Tumour margin	Pushing/well defined	Infiltrative/ill defined	Infiltrative/ill defined	Infiltrative/ill defined

*Table modified from The Royal College of Pathologists (RCPATH) Dataset for penile and distal urethral cancer histopathology reports, 2nd Edition 2015

References

- 1 World Health Organization (2016). *World Health Organization (WHO) Classification of tumours. Pathology and genetics of the urinary system and male genital organs*. Moch H, Humphrey PA, Reuter VE, Ulbright TM. IARC Press, Lyon, France.
- 2 Epstein JI, Cubilla AL, Humphrey PA (2011). *Tumors of the prostate gland, seminal vesicles, penis, and scrotum*. AFIP Atlas of Tumor Pathology. American Registry of Pathology, Washington DC, United States.
- 3 Velazquez EF, Melamed J, Barreto JE, Aguero F and Cubilla AL (2005). Sarcomatoid carcinoma of the penis: a clinicopathologic study of 15 cases. *Am J Surg Pathol* 29(9):1152-1158.
- 4 Slaton JW, Morgenstern N, Levy DA, Santos MW, Jr., Tamboli P, Ro JY, Ayala AG and Pettaway CA (2001). Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal lymph node metastasis in penile squamous cancer. *J Urol* 165(4):1138-1142.
- 5 Velazquez EF, Ayala G, Liu H, Chaux A, Zanotti M, Torres J, Cho SI, Barreto JE, Soares F and Cubilla AL (2008). Histologic grade and perineural invasion are more important than tumor thickness as predictor of nodal metastasis in penile squamous cell carcinoma invading 5 to 10 mm. *Am J Surg Pathol* 32(7):974-979.

- 6 Chaux A, Torres J, Pfannl R, Barreto J, Rodriguez I, Velazquez EF and Cubilla AL (2009). Histologic grade in penile squamous cell carcinoma: visual estimation versus digital measurement of proportions of grades, adverse prognosis with any proportion of grade 3 and correlation of a Gleason-like system with nodal metastasis. *Am J Surg Pathol* 33(7):1042-1048.

- 7 CAP (College of American Pathologists) (2013). Protocol for the examination of specimens from patients with carcinoma of the penis. Available from: <http://www.cap.org/ShowProperty?nodePath=/UCMCon/ContributionFolders/WebContent/pdf/penis-12protocol.pdf> (Accessed 1st March 2016).

- 8 Amin M.B., Edge, S., Greene, F.L., Byrd, D.R., Brookland, R.K., Washington, M.K., Gershewald, J.E., Compton, C.C., Hess, K.R., Sullivan, D.C., Jessup, J.M., Brierley, J.D., Gaspar, L.E., Schilsky, R.L., Balch, C.M., Winchester, D.P., Asare, E.A., Madera, M., Gress, D.M., Meyer, L.R. (Eds.) (2017). *AJCC Cancer Staging Manual 8th ed.* Springer, New York.