

57. Penis

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Emerging Prognostic Factors for Clinical Care

Histologic Subtypes

The subtypes of penile cancer have important prognostic implications, although the numbers of cases studied for some of the rarer subtypes are low and experience is limited to only very large centers around the world that see any reasonable amount of penile cancer cases. The prognostic importance of histologic classification lies in the fact that verrucous carcinoma, pseudohyperplastic carcinoma, and carcinoma cuniculatum have the best prognosis, and basaloid and sarcomatoid carcinomas have the worst prognosis. Warty and papillary carcinoma, not otherwise specified, have an intermediate prognosis.^{1,2} AJCC Level of Evidence: II

High-Risk Human Papillomavirus (HR-HPV)

High-risk genotypes—such as 16, 18, 31, 33, 45, and 52—have been associated consistently with penile cancer in approximately in 22–66% of cases based on upon histologic subtype.^{3,4} HR-HPV 16 and HR-HPV 18 are the most common genotypes implicated in penile cancer carcinogenesis. HR-HPV status is optimally ascertained using polymerase chain reaction assays when compared with the less sensitive *in situ* hybridization assay.^{3,5} Recently, HR-HPV status was shown to be an independent predictor of survival among penile cancer patients in one study from the Netherlands.⁵ AJCC Level of Evidence: II

p16ink4a (also known as p16)

The p16 protein is increased subsequent to the HR-HPV proteins' inactivation of the retinoblastoma gene. Its expression is measured via immunohistochemistry utilizing monoclonal antibodies and antigen-retrieval techniques. Two recent studies have shown that p16-positive tumors showing strong continuous nuclear and cytoplasmic expression exhibited either improved survival or lower recurrence rates among surgically treated patients with positive lymph nodes.^{6,7} AJCC Level of Evidence: II

Risk Assessment Models

The AJCC recently established guidelines that will be used to evaluate published statistical prediction models for the purpose of granting endorsement for clinical use.⁸ Although this is a monumental step toward the goal of precision medicine, this work was published only very recently. Therefore, the

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existing models that have been published or may be in clinical use have not yet been evaluated for this cancer site by the Precision Medicine Core of the AJCC. In the future, the statistical prediction models for this cancer site will be evaluated, and those that meet all AJCC criteria will be endorsed.

Recommendations for Clinical Trial Stratification

The following variables should be considered for stratification in future clinical trials for penile squamous carcinoma:

Primary tumor treatment

- T category \leq T2 versus \geq T3
- Grade 1–2 versus 3 or sarcomatoid
- Tumor size \leq 4 cm versus $>$ 4 cm

Management of regional lymph nodes/distant metastases

- Clinical Factors
 - Performance status
 - M0 versus M1 category
 - Nonpalpable/nonvisible (imaging) lymph nodes versus palpable or visible nodes
 - Inguinal lymph node size $<$ 4 cm versus \geq 4 cm
 - Unilateral versus bilateral inguinal adenopathy
 - Fixed mass
 - Pelvic metastases
- Pathological Factors
 - Number of positive inguinal nodes $<$ 3 versus \geq 3
 - Unilateral versus bilateral metastases
 - Extranodal extension of cancer
 - Pelvic nodal metastases

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