Review

Pathologic Evaluation and Reporting of Carcinoma of the Penis

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Abstract

Carcinoma of the penis is a rare tumor in the United States and in western European countries. Clinical management has become more complex in recent years, because organ-preserving strategies are being favored. Furthermore, our understanding of the pathogenesis of this malignancy has grown considerably. As a result of these developments, the demands on the pathology reports of surgical specimens from the penis have increased. There are also some peculiarities with the current World Health Organization and TNM classification systems of penile cancer as compared with other tumor entities. This review outlines the most relevant aspects that have to be considered in the pathologic handling and typing of penile carcinoma.

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Introduction

In the United States and in European countries, carcinoma of the penis is a rare tumor, with incidence rates ranging from 0.3 to 1.9 per 100.000 men.[1] A few decades ago, it seemed to be a rather simple oncologic disease: the tumor was usually visible, nearly all were diagnosed as squamous cell carcinomas, partial or total penectomy was the primary treatment of choice for every invasive cancer, and tumor spread was quite predictable, with the inguinal lymph nodes being the first metastatic sites.[2] However, it became evident that psycho-oncologic factors play a very important role in this tumor entity. Not only is the penis an important part of sexual actions, but also most of the male sexual characteristics in general are reflected in this organ. The loss of the penis or parts thereof affects sexual life and male self-assurance as well.[3] Today, organ-preserving surgical procedures are applied whenever possible.[4] Furthermore, it could be shown that cancer of the penis evolves from at least 2 different pathways, which are reflected by pathologic cancer subtypes.[5] Eventually, it became evident that the clinical course can be quite variable and that prognostic factors are clearly needed. Therefore, a close collaboration between clinician and pathologist is necessary for the optimal management of this tumor.

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Growth Patterns

Macroscopic inspection and gross sectioning identify 4 established growth patterns, which may influence surgical procedures and prognosis.[6,7] Verruciform tumors are exophytic, white to grey neoplasms, that are often associated with hyperkeratinisation. Superficial spreading carcinomas display a horizontal pattern of growth. Vertical tumors (Figure 1), on the other hand, are usually deeply invasive and sometimes ulcerated. Multicentric carcinomas consist of several independent tumor foci. A fifth pattern may be called "consuming tumor" and is observed in advanced cases, where the whole glans or even parts of the shaft have disappeared in the course of cancer growth.

Histologic Classification

It has been shown that cancer of the penis follows different pathogenetic pathways. About one-third of tumors are associated with human papillomavirus (HPV) infection, with the incidence varying among different countries.[8] Immunohistochemical detection of aberrant P16 expression serves as a surrogate marker for HPV-associated cancers.[9,10] Aside from HPV, chronic inflammation, such as Lichen sclerosus, may also predispose to penile cancer.[11] The new World Health Organization (WHO) histologic classification of carcinoma of the penis incorporates pathogenetic factors and mainly differentiates between HPV-associated cancers and non−HPV-related cancers (Table 1).[5]

Squamous cell carcinoma, usual type, is the most common cancer of the penis.[12] Among the other WHO subtypes, several are worth being discussed in more detail.

Verrucous carcinoma (Figure 2) is an extremely well-differentiated squamous neoplasia that is typically not related to

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HPV infection, and therefore is P16-negative.[13] It must be distinguished from exophytic HPV-associated tumors such as giant condyloma and warty carcinoma, and from papillary carcinoma, not otherwise specified, which is another non–HPV-related carcinoma.[14] It is very important not to apply the diagnosis of verrucous carcinoma to all tumors with any verruciform appearance, as pure verrucous carcinoma is thought to harbor no metastatic potential. A clue to the diagnosis is the base of the tumor, which typically shows a pushing kind of invasion and not an infiltrative pattern. This pushing front is even maintained in deeply invasive tumors, resulting in the subtype of carcinoma cuniculatum.[15]

Another well-differentiated, non–HPV-related penile tumor is pseudohyperplastic carcinoma. This entity typically occurs on the foreskin and is associated with lichen sclerosus.[16] Its distinction from reactive squamous hyperplasia is sometimes difficult.

Among the HPV-related cancers, basaloid carcinoma (Figure 3) is a poorly differentiated, aggressive neoplasm. It consists of solid nests, often with central, comedo-like necrosis. Basaloid carcinoma is typically P16-positive and frequently metastasizes to regional lymph nodes.[17] Warty carcinoma, another HPV-related tumor, is distiguished from its benign counterpart, condyloma acuminatum, by continous nuclear atypia, invasive growth, and the presence of high-risk HPV types.[18]

Tumor Grade

In general, grading of squamous cell carcinoma is not as straightforward as grading of adenocarcinoma, mainly because of 2 reasons: First, differentiation of tumor cells normally varies in any squamous proliferation from the base to the top. Second, grading criteria for squamous cell carcinoma are not as well defined as for adenocarcinoma. In a study among 7 pathologists dedicated to urologic malignancies, there was a poor interobserver agreement on grading of histologic specimens from penile carcinomas.[19] On the other hand, an exact histologic grading of penile cancer is important, because grading has been incorporated in the T-classification of this entity,[20] and it is a predictive factor for groin metastasis.[21] The new WHO classification of tumors of the penis does not dictate any specific grading system. Traditionally, the modified 4-tier Broder system has been used to grade squamous cell carcinomas of the penis.[22] Today, a 3-tiered system, as proposed by Velazquez et al, is preferred by most pathologists.[21]

T-Classification

The TNM system provides some peculiarities with the T-classification of penile cancer as compared with other locations.[20] The pT1 category is further subdivided into pT1a and pT1b. However, criteria for pT1b are not depth of invasion, as in other organs, but the detection of lymphovascular invasion or the presence of high-grade cancer. A great endeavor is demanded from the pathologist in this respect, as the distinction between pT1a and pT1b not uncommonly has an impact on the clinical decision of groin lymphadenectomy. Complete embedding of any pT1 tumor and meticulous microscopic investigation are necessary to rule out lymphovascular invasion. The intermixture of stage and grade in penile pT1 classification is unique in the TNM system, and a matter of discomfort among some pathologists, especially in the view of a lack of standardization of tumor grading. Infiltration of the erectile tissue is required for a pT2 category without distinction between the corpus spongiosum and the corpora cavernosa. However, it has been shown that there are differences in the metastatic rate between cancers affecting these 2 compartments.[23] In the pathology report, it should therefore be stated which spongy tissue is involved by the tumor.

Infiltration of the penile urethra is the single criterion for classifying a pT3-category. However, exact definitions for this parameter are not specified. Most pathologists would not diagnose a superficial carcinoma of the glans penis with an in situ involvement of the urethra as a pT3 cancer. Some fuzziness also exists with small cancers located directly at the meatus urethrae. In the author's view, only invasive cancers that infiltrated at least some part of the spongy body together with an involvement of the urethra should be classified as pT3 to avoid overtreatment.

Local Tumor Spread

Several patterns of tumor spread have been recognized, depending on the type and aggressiveness of the primary cancer.[24] Superficial cancers may take a horizontal route of spread along the mucosal surface either to the outer foreskin or into the urethra. A vertical spread through anatomic levels of the glans or through the penile fascia is found in deeply invasive tumors. A third route of spread is along the penile fascia, which then serves as a sort of guide rail for cancer growth, not uncommonly in a perineural fashion or along small vessels. The clinician and pathologist should be aware of this route of tumor spread because it may be a source for positive surgical margins.[24] The presence or absence of perineural invasion should be mentioned in the pathology report, because it is a prognostic parameter for groin metastasis.[21]

Surgical Margins

Histopathologic evaluation of surgical margins was an easy task in former times, when penectomy was the treatment of choice, usually with generous spaces between the tumor and the level of resection. The whole specimen was submitted, and a simple cross-section was performed by the pathologist to evaluate the margin. With partial penectomy, the corpora cavernosa and the corpus spongiosum containing the urethra are sometimes resected at different levels in order to reconstruct a urethral orifice that improves the patient's ability to pass water. This matter results in the necessity of different histopathologic sections to correctly evaluate the surgical margins. Today, organ-preserving surgery of the penis results in complex resection and reconstruction procedures, often with very close surgical margins.[25] Assessing complete resection often demands multiple, biopsy-like specimens from the surgical margins, which are often evaluated by frozen sections.[26] An integrated pathologic report that includes all specimens submitted must be given, referring to tumor classification and resection margins.

Lymph Node Metastases

Metastasis to the inguinal lymph nodes (Figure 4) is among the most important prognostic factors in cancer of the penis.[23] A meticulous processing of inguinal lymph node specimens is therefore mandatory. Sometimes, the sentinel technique with radioactive tracers is adopted to modify the extent of inguinal dissection.[27,28] When the lymph nodes are free of metastasis, the pathologist