Penile Carcinoma: Lessons Learned from Vulvar Carcinoma

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Purpose: Penile carcinoma is rare in the developed world and treatment guidelines are often based on marginal clinical data. Prospective controlled studies are virtually absent and meta-analyses are rare. Vulvar carcinoma, on the other hand, has many parallels to penile carcinoma, and the level of evidence for diagnosis and treatment is more robust. Therefore, we assessed the body of literature on vulvar carcinoma to identify potential improvements in the care of patients with penile carcinoma.

Materials and Methods: A literature review was performed on vulvar carcinoma and direct comparisons were made to a similar review of the literature on penile carcinoma.

Results: Several aspects of vulvar carcinoma management are clearly established and deserve closer evaluation in penile carcinoma. For example, human papillomavirus is identified in a high percentage of patients with vulvar carcinoma but is understudied in penile carcinoma. Further study is of potential clinical value, especially with the development of human papillomavirus vaccines for prevention. Penile carcinoma TNM staging does not adequately stratify survival or risk of advanced disease. Staging of vulvar carcinoma is dependent on tumor size and depth of invasion measured in millimeters, as opposed to the invasion of underlying structures in penile carcinoma. Management of the inguinal nodes is more refined for vulvar carcinoma, where lymphatic mapping has been conducted and sentinel node biopsy has proven to be highly effective in multicenter trials. Finally, the efficacy of adjuvant radiation and chemotherapy has been tested in controlled trials or reported in meta-analyses for vulvar carcinoma, which are both lacking for penile carcinoma. Radiation after inguinal node dissection, for example, has been shown to enhance survival in patients with defined risk factors. Neoadjuvant chemoradiation is recommended before surgery for advanced vulvar carcinoma.

Conclusions: Evidence derived from studies on vulvar carcinoma can be extrapolated to penile carcinoma to help guide clinical trials and future research directions to enhance the treatment of these patients.

Key Words: penile neoplasms; vulvar neoplasms; carcinoma, squamous cell; neoplasm staging; disease management

Abbreviations and Acronyms

DSLNB = dynamic sentinel lymph node biopsy

HPV = human papillomavirus

ILND = inguinal lymph node dissection

LN = lymph node

LND = lymph node dissection

PC = penile carcinoma

RCT = randomized clinical trial

RT = radiation therapy

SLNB = sentinel lymph node biopsy

VC = vulvar carcinoma

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PENILE carcinoma is a disease for which the treatment can be as devastating as the carcinoma itself. It is a rare disease in developed countries with a reported incidence in the United States of 0.58 in 100,000.[1] The incidence in Asia, Africa and South America is far higher, and accounts for 10% to 20% of all malignancies.[2] Due to its rarity, randomized prospective studies are virtually absent and meta-analyses are rare. Therefore, many controversies exist in the management of PC.

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Vulvar carcinoma in women has many similarities to penile carcinoma in men. Both diseases have similar anatomy, histology, risk factors and natural histories. Although VC is also relatively rare in developed countries (2.5/100,000 in the United States), it is a much better studied disease, with a higher level of evidence for guiding diagnosis and treatment.[3] We propose that the body of literature on VC can be used to guide us toward improvement in the management of PC.

ANATOMICAL SIMILARITIES

The male and female external genitalia develop along a common embryological pathway. The lymphatics from the glans of the penis as well as the clitoris, labia minora and the terminal end of the vagina drain into the deep inguinal nodes and the internal iliac nodes.[4] The penile shaft skin and the labia majora drain into the superficial inguinal nodes. The penis and vulva differ in that the penis often drains bilaterally and the vulva drains unilaterally, except for the midline regions of the vulva.[4] Metastatic spread in vulvar and penile carcinoma via these lymphatics occurs in a predictable pattern without skip lesions. The presence or absence of lymph node metastasis in PC and VC is highly predictive of survival.

HISTOLOGY AND HPV ASSOCIATION

Penile and vulvar cancers have previously been considered diseases of the elderly with a peak incidence in the sixth and seventh decades. This concept is changing with studies showing a quarter of patients with penile cancer to be younger than 50 years old.[5] A similar decrease in the age of diagnosis has occurred in VC, for which the average age is 55 years.[6]

Squamous cell carcinoma is the most common malignancy in penile and vulvar carcinoma, accounting for 90% to 95% of cases. There are 2 main categories of well studied predisposing factors to PC that are paralleled in VC. The first is the HPV related pathway that is associated with HPV 16, 18 and 33. The second is a HPV unrelated pathway that is secondary to chronic inflammation such as lichen sclerosus in VC and balanitis xerotica obliterans in PC. These are considered synonymous conditions characterized by a chronic, progressive, atrophic, sclerosing process found on male and female genitalia. A systematic review of 31 studies including 1,466 men showed that HPV is associated with penile carcinoma in 47% of patients.[7] Similar studies have found 60% of vulvar carcinoma to be associated with HPV.[8]

The high rate of HPV association with PC raises the question of the usefulness of the HPV vaccine in males. It is well recognized that the HPV vaccine can effectively reduce the risk of preinvasive cervical and vulvar intraepithelial neoplasia.[9] Until recently there was still no defined role for the use of the HPV vaccine in boys due to the lack of long-term studies on the efficacy, safety and cost-effectiveness of the HPV vaccine. However, a randomized placebo controlled trial of more than 4,000 males age 16 to 26 years found the HPV vaccine (HPV 6, 11, 16, 18) reduced the incidence of external genital lesions by 90.4%.[10] Earlier this year the American Academy of Pediatrics recommended the routine use of the quadrivalent HPV vaccine in boys ages 11 and 12 years, and all boys age 13 to 21 who had not previously been offered the vaccine. Their recommendations were backed by clinical trials showing the vaccine is highly immunogenic, safe and well tolerated by boys and girls alike. The vaccine could prevent up to 47% of PC, 87% of anal cancer and 60% of oropharyngeal cancer, and prevent the transmission of the virus to female partners.

STAGING

TNM staging of PC is often criticized as being poorly predictive of patient outcome. The TNM staging of VC differs significantly from that of PC and it is possible that it could guide changes to PC staging to improve prognostic value. The principal shortcoming of the TNM system in PC is that it does not adequately stratify the risk of death. In one study there was no significant difference between survival for Tis/Ta and T1, and several studies have shown that the 5-year survival for T3 is the same or better than that for T2 disease.[11] This finding is likely due to the combination of corpus spongiosum and corpus cavernosum into 1 stage (T2), because the ability of a tumor to invade the tunica albuginea and, therefore, into the corpus cavernosum has been postulated to be a marker of aggressiveness with worse prognosis.[12] Stage T3 also combines invasion anywhere along the entire length of the urethra and into the prostate. Invasion into the distal urethra, especially at the glans, has a better prognosis than invasion into the proximal urethra or corpus cavernosum.[11] The prostate is rarely involved in PC and the prognostic value of invasion into the prostate has not been determined.[11]

The recent update to the TNM staging split T1 into T1a and T1b based on the absence or presence, respectively, of lymphovascular invasion. On multivariable analysis this has been shown to be an independent predictor of positive LNs in patients with clinically negative LNs.[13] The updated TNM staging also includes grade to differentiate between T1a and T1b (absence or presence of high grade carcinoma). While grade is widely accepted as an important risk