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# Immunotherapy and penis cancer

## Abstract

Penis cancer, a cancerous disease in which malignant cells appear in the tissues of the penis. It occurs in the uncircumcised older men. It is recognized by at least two independent carcinogenic routes: virus and non-virus induced. The penis cancer is also very rare in Europe and North America. In the United States, penis cancer generally occurs in less than 1 man in 100,000 and accounts for less than 1% of cancer in men. Around half of the cancers are mainly caused by an infection with high risk human papilloma virus (hrHPV), and its main type is HPV-16. The other types of penis cancer arise, independent of hrHPV infection. The most common symptoms of penis cancer are irregular swelling at the end of the penis, a growth or sore on the penis, skin thickening on the penis, changes in the color of the penis, small and crusty bumps beneath the foreskin, reddish and velvety rash beneath the foreskin, and pain in the shaft or tip of the penis. Squamous cell or epidermoid carcinomas, basal cell carcinoma, melanoma and sarcoma are different types of penis cancers which are usually rare. The immunotherapy is a good alternative of chemotherapy for the treatment of penis cancer, but maximum drugs and therapies are under the clinical trials for FDA approval.

**Keywords:** penis cancer, merkel cell carcinoma, squamous cell or epidermoid carcinomas, basal cell carcinoma, melanoma and sarcoma, genital warts, penile injury, and psoralen high risk human papilloma virus (hrHPV)

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**Abbreviations:** AIN, anal intraepithelial neoplasias; CR, complete response; HIV, human immunodeficiency virus; HPV, human papilloma virus; hrHPV, high risk human papilloma virus; PIN, penis intraepithelial neoplasias; RCT, randomized controlled trials; RR, recurrence rates; VIN, vulvar intraepithelial neoplasias

## Introduction/Epidemiology

Penis cancer is when the malignant cells appear in the tissues of the penis. Approximately 95% of penile cancers are squamous cell carcinoma. Othertypes; of penis cancer like melanoma, small cell carcinoma, Merkel cell carcinoma are usually rare.[1] The penis cancer is also very rare in Europe and North America. In the United States, penis cancer generally occurs in less than 1 man in 100,000 and accounts for less than 1% of cancer in men. However, penis cancer is much more common in some regions of South America, Africa, and Asia, where it holds for up to 10% of cancers in men.[2] According to the National Cancer Institute, in the year 2014 in United States, 1,640 new cases were estimated. Additionally, in the same year, 320 death cases were also estimated.[3] As per the statistical analysis, the age-standardized incidence of penis cancer is much higher in non-Western world. It signifies 10-20% of cancerous disease in men, ranging from 0.7 to 3 per 100,000 persons in India to 8.3 per 100,000 men in Brazil, and even higher in Uganda, where it is usually diagnosed. The penis cancer is a very rare cancer among all the male cancers, with higher incidences observed in between the age of 75-84 years.[2,4]

## Etiology/Predisposing Factors

Generally, penis cancer occurs in the uncircumcised men. Circumcision is the elimination of the foreskin,and may decrease the chances of penis cancer.[5] The different types of penis cancer are as follows:[5]

a. **Epidermoid/squamous cell carcinoma:** About 95% of the penile cancers are squamous cell or epidermoid carcinomas. The epidermoid carcinoma can initiate anywhere on the penis; though, it normally develops on or under the foreskin.

b. **Basal cell carcinoma:** Below the squamous cells in the lower epidermis, are round cells, known as basal cells and occasionally, these can transform into malignancy. It is a type of non-melanoma skin cancer, which represents less than 2% of penis cancer.

c. **Melanoma:** Although, this type is the rarest subtype of penile cancer, it is the one with the worst prognosis.

d. **Sarcoma:** Sarcoma accounts for about 1% of penis cancer. These are the cancers that develop in connective tissues, such as fat, muscles, and blood vessels.

The most common symptoms of penis cancer are irregular swelling at the end of the penis, a growth or sore on the penis, skin thickening on the penis, changes in the color of the penis, small and crusty bumps beneath the foreskin, reddish and velvety rash beneath the foreskin, and pain in the shaft or tip of the penis.[5] There are common risk factors of penis cancer, such as age, smoking, HPV infection, phimosis, HIV infection, genital warts, penile injury, and psoralen – UV-A chemotherapy.[2]

## Pathophysiology/Molecular basis

In the molecular concept, the penis cancer is recognized by at least two independent carcinogenic routes: virus and non-virus induced. Around half of the cancers are mainly caused by an infection with high risk human papilloma virus (hrHPV), and its main type is HPV-16.[6–11] The other types of penis cancer arise, independent of hrHPV infection.[12] However, the molecular routes of disruption vary in many ways, which is particularly related to the early genetic events and the activity of the known viral oncogenes, E6 and E7. The various common cellular pathways are disrupted at the earlier and later stages during the penis cancer , in both the virus and non-virus induced types of cancer . The penis cancer is likely to be initiated through the interference with the cellular $p16^{INK4a}$/cyclin D/Rb pathways or $p14^{AER}$/MDM2/p53, either by viral (HPV) or non-viral (mutation) mechanism. This might result in an uncontrolled division of cells, and may also trigger a state of chromosomal instability, which further drives the carcinogenic process. The metastasis, angiogenesis,

invasion, and expression of genes involved in disease progression, are the common molecular events that are associated with the later stages of penis cancer.[13] The molecular basis of penis cancer has been explained in Table 1 below.

**Table 1** Molecular concept of Penis cancer[13]

| Cancer | Carcinogenic routes | Early molecular events | Leading to disruption of | Resulting in | Later molecular events | Resulting in |
|---|---|---|---|---|---|---|
| Penis Cancer | HPV induced | Viral oncogenes, hrHPV E6 and hrHPV E7 | p14 / MDM2 / p53 and p16 / cyclin D / CDK / Rb | Uncontrolled cell division and reduced apoptosis. | Altered gene expression involved in disease invasion, progression, metastasis, and angiogenesis. a.o.Ras, Myc, Telomearase, E-cadherin, MMPs, COX, PGE2 synthase | Immortalization, Angiogenesis, metastasis, and invasion |
| | Non-virus induced | Oncogenes activating and/or TSG inactivating mechanism such as gene promotor methylation, gene overexpressi-on, and gene mutation. | | | | |

## Immunotherapy

### Monoclonal antibody

**Cetuximab**: Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor and a recombinant chimeric monoclonal antibody, which has been successfully used in the treatment of the Non-small cell lung cancer, colorectal cancers and squamous cell skin cancer (Non-FDA approved).

**Non-FDA approved MAB drugs**

Table 2

### Vaccine

**Non-FDA approved vaccine**

Table 3

**Table 2** Non-FDA approved monoclonal antibodies[14]

| Drug | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| Cetuximab | NCT02014831 | Phase II | Randomized, Open Label, Safety/Efficacy Study | EGFR |

**Table 3** Non-FDA approved HPV vaccine[15]

| Drug | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| HPV16 E7 | NCT02379520 | Phase I | Open Label, Safety Study | Cancer cells |

**Aldara immunotherapy:** Aldara (Imiquimod) is a prescription medication, which works as an immune response modifier. The use of Aldara in penis intraepithelial neoplasias (PIN), vulvar intraepithelial neoplasias (VIN), and anal intraepithelial neoplasias (AIN) were supported by two cohort studies. About15 cases have been reported for PIN, and 3 cases have been reported for AIN. There are 8 uncontrolled/ cohort studies, 9 case reports, and 2 randomized controlled trials (RCTs) for VIN. In a combined study of randomized clinical trials, uncontrolled and cohort studies, the mean complete response (CR) rates for PIN, AIN and VIN were 70%, 48% and 51% ,respectively, and the mean partial response (PR) rates for PIN, AIN, and VIN were 30%, 34%, and 25% respectively. The recurrence (RR) rates for PIN, AIN, and VIN were 0%, 36%, and 16%, correspondingly. The follow-up periods for PIN, AIN, and VIN ranged from 10 to 12 months, 11 to 39 months, and 2 to 32 months, respectively. Though, the result of PIN was best between AIN and VIN. The drug, Aldara was practically well tolerated, with different side-effects being managed with decrease in the rate of drug usage. Due to these outcomes, Aldara seems to be a safe and effective drug, and as an alternate for the treatment of penis cancer.[16]

### Adoptive Immunotherapy

**Non-FDA approved adoptive therapy**

Table 4

### Miscellaneous

**Non-FDA approved miscellaneous drugs**

Table 5

**Table 4** Non-FDA approved Adoptive therapy[19-21]

| Drug | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| E6 TCR | NCT02280811 | Phase II | Safety/Efficacy Study, Open Label | Cancer cells |
| Young TIL | NCT01585428 | Phase II | Non-Randomized, Open Label, Safety/Efficacy Study | Cancer cells |
| HPV 16 E7 peptide | NCT00019110 | Phase I | Treatment | Cancer cells |

**Table 5** Non-FDA approved miscellaneous drugs[22, 23]

| Drug | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| BBI608 | NCT01325441 | Phase I, II | Non-Randomized, Open Label, Safety/Efficacy Study | Cancer stemness cell |
| IGF-methotrexate | NCT02045368 | Phase I | Open Label, Safety Study | IGFR |

## Conclusion

Penis cancer has lower incidence in comparison with other cancers. Penis cancer commonly affects the older men, so the treatment should not be aggressive. The immunotherapy may be a good alternative of chemotherapy for the treatment of penis cancer. Currently the modified dose and regiment of the treatments are under the clinical trials for FDA approval. HPV vaccine has been suggested as a preventive option for penile cancer. Proper pre-clinical and clinical designs of these vaccines are the important pillars in understanding the future of immunotherapy in treating cancer patients.

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## Conflicts of interest

Authors declare that there is no conflict of interest.

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