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Review Article

Penile carcinoma: Multi-options possible requirements

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ABSTRACT

There is a relatively higher incidence of penile cancer in India 3.32 per 100 000 men, whereas Jewish men have the lowest incidence. The risk factors include phimosis, balanitis, and no circumcision. Human papillomavirus accounts for 40% of cases. Other factors include obesity, smoking, Psoralen UV- A therapy. Penile cancer is common above the age of 50 years. 95% of penile cancer is a squamous cell, carcinoma. Treatment of Penile carcinoma is stage wise, where surgery, partial or total penectomy, radiation therapy, or chemotherapy are a mainstay. Laser therapy is often used in the treatment of both CIS and low-grade/stage invasive disease. The neoadjuvant regimen often used is TIP, which consists of 4 cycles of paclitaxel, ifosfamide, and cisplatin. Nimotuzumab EGFR-antibody treatment as an alternative salvage treatment for advanced penile cancer. Immune Checkpoints blockades such as cabozantinib are evaluated in resistant diseases. Avelumab is currently tested in penile cancer patients in two ongoing trials.

1. Introduction

In the age group between 50 and 70 years, penile cancer is more prevalent, with a mean age of 67 years in some countries. The common penile malignancy is squamous cell carcinoma, which originates from the non-keratinized epithelium of the glans or the inner layer of the prepuce.[1] The main types of HPV found in men with penile cancer are HPV 16, 18, 22, 31, 33, and 45. More than 20% of patients with penile cancer have been tested positive for HPV infection. Patients with HIV have an 8-fold increased risk. In uncircumcised men, Phimosis is the causation of penile cancer as smegma may be a precipitating factor. HIV and AIDS may be precipitating factors.[2] The link between obesity BMI of >30 kg/m^2. and penile cancer is well-known. 3.6 % of new cancers were attributed to high BMI. Caused by increased insulin and cortisol levels, with chronic inflammation.[3] One of the strong links of Squamous cell carcinoma of the penis {SCC} is chewing tobacco or smoking. A clear dose-relationship response for smoking and chewing was observed.[4] PUVA poses an increased risk of squamous cell carcinoma on non-sun-exposed skin, few studies have examined its specific association with penile cancer.[5]

2. Grading of Penile Cancer

1. Grade X Grade cannot be accessed.
2. Grade 1 Low-grade cancer.
3. Grade 2 Moderate to High grade cancer.
4. Grade 3 High-grade cancer with metastasis.

3. Investigations

Medical history and physical exam: To evaluate symptomatology of Penile carcinoma.[6]

The membrane protein caveolin-1 (CAV1). CAV1 levels strongly increase in malignant epithelial cells, which was

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Table 1: Signs and symptoms of penile cancer.

Growth or sore on the penis which does not heal within four weeks with bleeding or no bleeding.
Foul-smelling discharge and rash on the penis.
Thickening of the skin of the penis or Phimosis and change in the colour of the skin of the penis or foreskin.
Penile ulceration, with fungating mass in severe cases.

correlated with worse clinical outcomes.

The diagnosis of penile cancer is confirmed through biopsy.

Incisional and Excisional biopsy of Lesion: If the lesions are small such as nodule or lump done under local anesthesia.

Fine needle aspiration or CT guided needle biopsy: enlarged lymph node biopsy.

Chest X-ray: done to observe if cancer has spread to the lungs.

MRI helps in the detection and extent of inguinal and pelvic lymphadenopathy.[7]

Treatment of Penile carcinoma: Penile cancer is a highly curable disease when diagnosed on early-stage (0, I, and II stages), instead of advanced disease (III and IV stage) which remains hard to cure. Treatment of metastatic SCPC is associated with poor outcomes with a median OS of 6-12 months.

Early localized penile carcinoma has an excellent outcome with more than 70% long-term survival with local penile conservative approach using surgery or radiotherapy. About 30-40% of patients present with lymph node metastases in which long-term survival is just 20-30%.[8]

3.1. Stages of penile cancer and treatment

3.2. Topical treatment of non-invasive penile cancer

The two main topical treatments for non-invasive penile cancer are 5-fluorouracil (5-FU) and IQ {Imiquimod} 5 Fluoro Uracil exerts its chemotherapeutic effects through inhibition of the enzyme thymidylate synthetase. IQ is an immuno-modulating drug that acts on several levels of the adaptive immune system. It activates the cells of this aspect of the immune system through toll-like receptor 7 (TLR-7) causing secretion of cytokines such as interferon-alpha, interleukin 6 (IL-6) and tumour necrosis factor-alpha. The treatment is usually given 5 days a week for a period of 4 to 6 weeks. CIS penile cancer up to 57% of patients reported a complete response with a low number of adverse events. The common adverse effect is local skin irritation at the application site, headache, flu-like symptoms, and myalgia.[10]

In patients with metastatic disease, chemotherapy is undoubtedly the only possible effective treatment.

3.3. Adjuvant Chemotherapy

The adjuvant setting refers to chemotherapy after complete surgical treatment of the local disease and inguinal lymph node metastases.

This treatment is indicated after the removal of affected lymph nodes vincristine/bleomycin/ methotrexate combination treatment is usually administered.

3.4. Neoadjuvant chemotherapy

For patients with palpable lymph nodes and especially with large, immobile inguinal nodal metastases, recent studies have shown promising results for neoadjuvant chemotherapy. (vincristine/bleomycin/ methotrexate, Cisplatinum/bleomycin/methotrexate, cisplatinum/5-FU or cisplatinum/irinotecan) are used.

Advanced penile cancer holds a poor prognosis and must be approached via a multimodal treatment regimen that includes neoadjuvant chemotherapy followed by surgical resection.

3.5. Therapeutic and palliative chemotherapy in advanced metastatic penile cancer

The following chemotherapeutic regimens are employed:

3.6. Intraarterial chemotherapy

The infused regimens are composed of methotrexate (110 $mg\,m^{-2}$ per day), mitomycin C (4.5 $mg\,m^{-2}$ per day), bleomycin (15 $mg\,m^{-2}$ per day), cisplatin (35 $mg\,m^{-2}$ per day), and 5-fluorouracil (1200 $mg\,m^{-2}$ per day) These drugs were infused continuously by using the pump for 2 days in each course. The course was repeated at an interval of 4 weeks. This may be used as neoadjuvant therapy in most cases.[14]

3.7. Mode of action of cetuximab and Panitumumab

Cetuximab and Panitumumab are two distinct monoclonal antibodies (mAbs) targeting the epidermal growth factor receptor (EGFR).

4. Curative Radiotherapy

Represents an alternative to primary surgical resection for SCC, when surgery is not appropriate. RT may provide a palliative benefit after chemotherapy. High dose (60Gy) required, with significant adverse events. Palliative radiation remains the standard in unresectable inguinal lymph node metastases. Radiation treatment of the primary tumour is an alternative organ-preserving approach with good results in selected patients with T1-2 lesions < 4 cm in diameter. Radiotherapy results are best with penile brachytherapy with local control rates ranging from 70-90%. External beam radiotherapy and brachytherapy are

Table 2: Therapy of penile canceras per stage. [9]

Stag es of Penile Cancer	Clinical Picture	Therapy
Stage 0	Carcinoma in situ (CIS) and verrucous carcinoma	Ca In situ: circumcision. local therapy (laser ablation, topical 5-FU or imiquimod, or cryotherapy) verrucous carcinoma - laser therapy, Mohs surgery, wide excision, or cryotherapy.
Stage 1	Superficial layers are involved	Glansectomy, or removal of part of the penis. Radiation therapy or laser ablation
Stage 2	Deep into the tissues of the penis (such as the corpus spongiosum or cavernosum) – no lymphatic spread	Partial or total penectomy
Stage 3	Deep into the tissues of the penis (such as the corpus spongiosum or cavernosum) – lymphatic spread	Chemotherapy (chemo) or chemo plus radiation
Stage 4	The main tumor has grown into nearby tissues, like the prostate, bladder, scrotum	Chemo plus radiation

Table 3: Chemotherapeutic regimens.

Lines of Therapy in Penile Carcinoma based on various studies. [11–13]

First Line Therapy	Second Line Therapy	Third Line Therapy
Cisplatin 75 mg/m2 (70-80) Day 1, 5 Fluorouracil 800-1000 mg/m2 for 4 days, Every 3-4 weeks	5FU/Mitomycin	Weekly Paclitaxel
Cisplatin or Carboplatin with capecitabine	Carboplatin/Paclitaxel	Immunotherapy
Vincristine + Methotrexate	Sunitinib or Sorafenib	Newer Investigational Drugs
Paclitaxel 175 mg/m2 on day 1 Ifosfamide 1,200 mg/m2 on days 1 to 3 , Cisplatin 25 mg/m2 on days 1 to 3	Intraarterial cisplatin + Gemcitabine	
Irinotecan (60 mg/m2) on days 1, 8 and 15 Cisplatin (80mg/m2)		
Cisplatin 8.5 mg m–2 Methotrexate 275 mg m–2 Mitomycin 1.2 mg m–2 Bleomycin 4 mg m–2.		
Cetuximab + Cisplatin or Panitumumab (6 mg/kg, repeated every 2 weeks) (anti-EGFR monoclonal antibodies, with 50% of them showing a response to treatment, and a median PFS of ~ 3 months)		
Paclitaxel Epidermal growth factor receptor monoclonal antibody, nimotuzumab		
Anti-CTLA-4 agent Ipilimumab Anti-PD-1 agent nivolumab administered at standard doses was associated with a prominent response in a patient refractory to paclitaxel, Ifosfamide and cisplatin Cemiplimab - (PD-1) inhibitor given intra-venously (3 mg/kg every 2 weeks) used for Cisplatin Resistant Metastatic Penile Cancer.		
Paclitaxel Epidermal growth factor receptor monoclonal antibody, nimotuzumab IgG1 antibodies bind to PD-L1 to inhibit PD-1.		

No clinical benefits were observed with Gefitinib or Erlotinib.

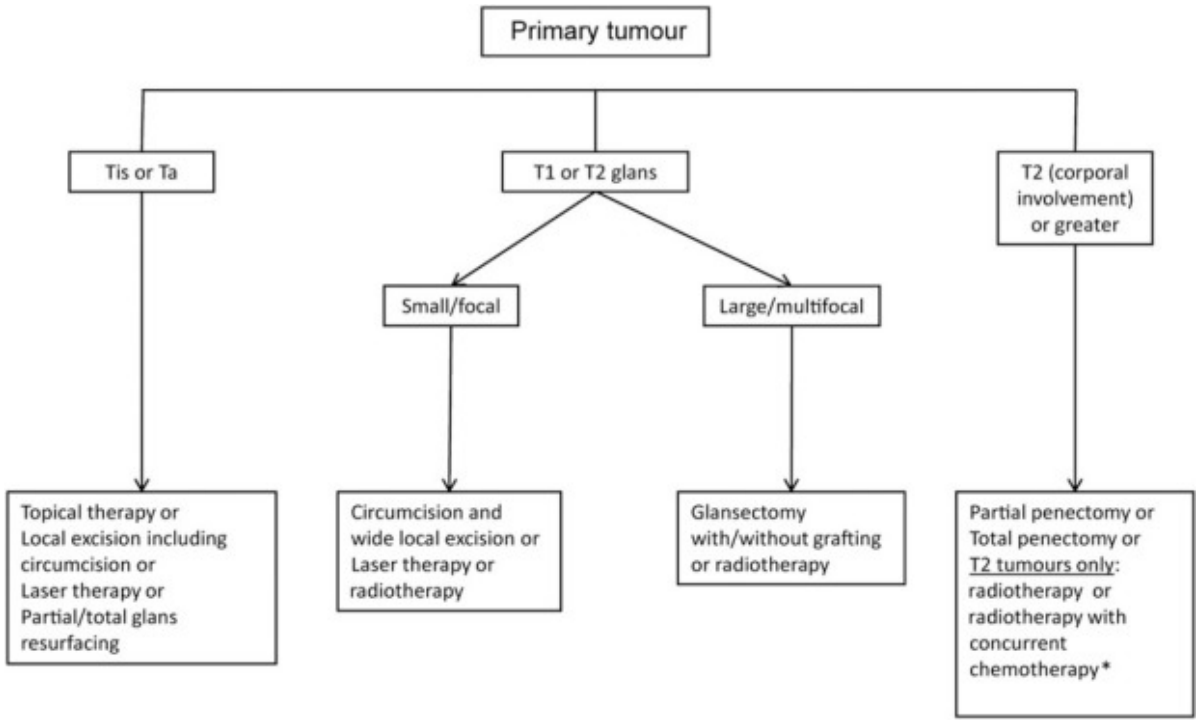

Fig. 1: Algorithm for treatingpenile cancer.

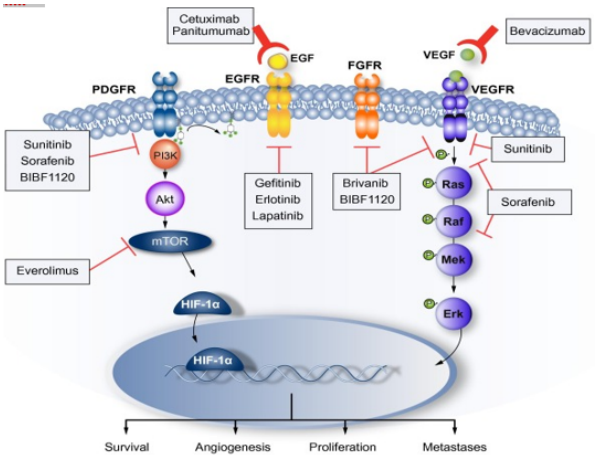

Fig. 2: Action of Mabs

associated with severe complications down the line, such as urethral stenosis, telangiectasia, fibrosis/atrophy, and penile necrosis. Local brachytherapy achieves lower local control rates compared to surgical treatment (70–90% versus 90–92% and 94–96% for glansectomy and glans resurfacing.[15,16]

4.1. Surgical manipulation

Radical surgery (partial or total penectomy with a negative surgical margin) remains the gold standard in managing invasive penile cancer.

Table 4: Surgical procedures

1. **Sentinel lymph** node biopsy is the first node to receive the drainage directly from a tumor. Detection and pathological examination of the SLN is an important oncological procedure that minimizes morbidity related to extensive nodal dissection.
2. **Circumcision** is generally recommended in men with CIS (carcinoma in situ). Circumcision is the surgical removal of the skin covering the tip of the penis.
3. **Mohs surgery**, thin layers of cancer-containing skin are progressively removed and examined until only cancer-free tissue remains. Mohs surgery removes the smallest amount of healthy tissue, which minimizes scarring.
4. **Laser therapy** has been used in the treatment of both CIS and low-grade/stage invasive disease. Its palliative surgery and is used for out patients.
5. **Glans resurfacing** is a feasible organ-preserving surgical option in correctly selected patients for both malignant and benign penile disease
6. **Total glansectomy**: the excision of the glans penis from the corporal heads. Glansectomy with split-thickness skin graft reconstruction is a safe and effective treatment for men with localized penile cancer.
7. **Penectomy** is an operation to remove all or part of a penis. Radical penectomy is indicated in most T3 and all T4 staged penile tumours.

4.2. Psychological support

Depression and even suicidal thoughts are not uncommon in penile cancer sufferers, and this is an established field of study. Post-traumatic stress disorder (PTSD) could have important relevance. Sexual function was severely affected in patients treated with partial penectomy.[17,18]

5. Conclusion

Penile carcinoma commonly occurs in the 6^{th} or 7^{th} decade of life**,** comes under the category of rare cancer but serious disease. The treatment of penile cancer is Stage-adapted treatment. Treatment Cycles generally last about 3 to 4 weeks. Some of the drugs used to treat penile cancer include: Cisplatin, Fluorouracil (5-FU). Paclitaxel Ifosfamide, Mitomycin C, Capecitabine. Often, 2 or more of these drugs are used together to treat penile cancer Prognosis is poor for patients with platinum refractory disease, with mOS of < 6 months.

Adjuvant radiation therapy must be considered for high-risk squamous cell carcinoma. The combination of cisplatin and 5-FU in neoadjuvant therapy improved the response rates up to 80% with 40% complete responses. PD-1 inhibition is now the standard of care for advanced squamous cell carcinoma. Platin-based chemotherapy or anti-EGFR can be prescribed in the second-line setting.

Surgery is the treatment of choice whenever the tumor is resectable. The glans penis is the most common site of penile cancer with 50% of newly diagnosed lesions isolated to the glans and 80% isolated to the glans and prepuce. Younger patients are often offered more penile-sparing approaches for primary tumors but more aggressive treatment such as lymphadenectomy for nodal disease. Glansectomy is indicated for larger or more advanced lesions. Side effects of surgery include erectile dysfunction, pain, discomfort, altered appearance, bleeding, trouble urinating, swelling, itching and lymphoedema. Quality of life post-surgery for penile cancer has shown that up to 40% of patients had a poor quality of life. In India 5 year survival rates were found to be 87% and 60% respectively in stage I and II respectively.

6. Conflict of Interest

The authors declare no relevant conflicts of interest.

7. Source of Funding

None.

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