AUA Update Series 2020
Lesson 8
Volume 39

Treatment of Early Stage Squamous Cell Carcinoma of the Penis*

Learning Objective: At the conclusion of this continuing medical education activity, the participant should be able to evaluate early stage penile cancer, and be familiar with the epidemiology, risk factors and variety of options and algorithms used to treat early stage penile cancer.

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Release date: March 2020

Expiration date: March 2023

KEY WORDS: penile neoplasms; carcinoma, squamous cell; administration, topical; conservative treatment; laser therapy

EPIDEMIOLOGY, RISK FACTORS AND NATURAL HISTORY

Penile cancers are rare but often aggressive neoplasms that affect less than 1% (0.4% to 0.6%) of the total male population in Europe and the United States.[1] However, the prevalence of the disease varies in different geographical regions with rates as high as 10% in some developing countries.[2-4] Prevalence is lower in countries that practice neonatal circumcision, promote HPV vaccination, and have high levels of health care awareness and socioeconomic standards that allow for routine hygiene to prevent phimosis.[5] The tumor most commonly develops at the penile foreskin or glans.[2] The incidence of primary malignant penile cancer increases with age, especially after the 6th decade of life.

Epidemiological analysis using the SEER (Surveillance, Epidemiology, and End Results) database indicates that black men have a significantly higher incidence of primary malignant penile cancer (0.90/100,000) compared to white men (0.70/100,000) or men of other races (0.34/100,000). Risk factors for squamous cell carcinoma of the penis include HPV infection, poor genital hygiene, multiple sexual partners, male-with-male anal intercourse, lack of circumcision,[2] tobacco use[6] and heavy alcohol consumption.[7] The risk of a penile tumor is proportionate with a higher median duration of HPV infection.[8] The Centers for Disease Control and Prevention recently found that HPV associated penile cancers are more likely to develop in black and Hispanic men than in white and non-Hispanic men.[9]

DIAGNOSIS

Diagnosis begins with a thorough physical examination. The lesion is assessed for size, location and involvement of the corporal body or urethra. Inguinal lymph nodes must be palpated for lymphadenopathy. Examination of the scrotum and base of the penis is also required to evaluate for possible tumor involvement. Definitive diagnosis is achieved through tissue sampling/excision, as penile cancers might be confused with non-cancerous lesions. Imaging is often required to determine the extent of tumor invasion and inguinal lymph nodes, as relying only on palpation and physical examination can result in false-negative findings,[10] especially in obese patients.

de Vries et al recommend combining physical examination with Doppler ultrasound to determine whether organ sparing techniques can be performed in potential candidates.[11] Magnetic resonance imaging with or without artificial erection is also used for local staging in cases of organ preserving surgery.[12] Computerized tomography of the chest, abdomen and pelvis is typically performed to evaluate the spread of cancer to the lymph nodes and more distant locations.[13] It is important that the scan go through the mid thigh to ensure the groin is included on the radiology interpretation.

TOPICAL THERAPIES

Topical treatments, cryotherapy, circumcision, laser and photodynamic therapy are often used as first line treatment options for non-invasive and early stage penile malignancies (carcinoma in situ, Ta and T1).[14] Topical treatment has been suggested to be the most effective for early stage penile cancer given that surgical resection and systemic chemotherapy may be unnecessary.[15] The most common chemotherapeutic compounds for topical application for early stages of penile cancers are fluorouracil and imiquimod.

The use of 5-FU is widely accepted for treatments involving early stage penile condylomas and carcinoma in situ.[16] Its mechanism of action is through interference with DNA replication, principally as an inhibitor of the enzyme thymidylate synthase. Once administered topically 5-FU enters the cells where it undergoes ribosylation and phosphorylation, resulting in an end product that resembles a nucleotide. 5-FU then binds to thymidylate synthase through cofactor 5,10-methylene tetrahydrofolate, thus inhibiting the methylation process of deoxyuridine monophosphate to thymidine monophosphate. This process leads to scarcity of available thymidine, which limits DNA synthesis, reduces cell growth and eventually causes cell death.[17] In terms of treatment outcomes there is no superior topical treatment modality. The treatment of choice depends on patient tolerance of treatment and physician level of comfort with the available therapeutic options.[16] Side effects of topical 5-FU are usually rare and mild, and include application site reactions (such as redness, dryness, burning, erosion, pain, irritation and swelling), headache, allergy and upper respiratory infection.[15]

Imiquimod is a 5% topical that can be used topically due to its molecular size and hydrophobic nature.[18] It primarily inhibits tumor growth through activating Toll-like receptor 7, which is expressed on hematopoietic cells such as plasmacytoid dendritic cells and B cells. Upon activation imiquimod promotes secretion of cytokines, interleukin 6 and tumor necrosis factor-α, and acts by reducing interleukin 10 signals,[19, 20] thereby inhibiting tonic anti-inflammatory signals.[21] Evidence for the use of topical IQ for penile cancer is scarce and outcomes are mixed.

Deen and Burdon-Jones conducted a review of 22 case reports and 7 small case series in which IQ was used to treat penile intraepithelial neoplasia.[22] Of a total of 48 patients 32 presented with Erythroplasia of Queyrat, 8 with Bowen's disease and 8 with bowenoid papulosis. Complete and partial response occurred in 30 (62.5%) and in 4 (8%) patients, respectively, and 14 (29%) had no response. Treatments given fewer than 4 times weekly appeared to bestow a longer duration of complete response (81%), although the duration of treatment was extended (mean 113 days). Treatments given more than 4 times weekly (mean duration 53 days) resulted in a complete response rate of 68%. The number of studies in this review were heterogeneous in terms of duration of treatment, frequency of application and follow-up. This heterogeneity and the variations in outcomes make drawing unbiased conclusions on the efficacy of IQ difficult. The most common adverse reactions associated with IQ are skin irritation at the application

ABBREVIATIONS: 5-FU (fluorouracil), HPV (human papillomavirus), IQ (imiquimod), PDT (photodynamic therapy), YAG (yttrium-aluminum-garnet)

site, headache, flu-like symptoms and myalgia. The U.S. Food and Drug Administration has approved the use of imiquimod under the name Aldara™ for the treatment of external genital and anal warts in adults.

Alnajjar et al retrospectively reviewed 44 cases of penile carcinoma in situ treated with topical agents.[15] First line therapy was 5-FU and the second line topical agent was IQ. At a mean follow-up of 34 months complete resolution was reported in 25 cases (57%), partial response in 6 (13.6%) and no improvement in size or visibility in the remaining 13 (29.5%). In addition, adverse events were reported in 12% of the subjects after the administration of 5-FU and local toxicity in 10%. In a retrospective study of 86 patients with penile carcinoma in situ and follow-up greater than 10 years the complete response rate was 50% for topical 5-FU vs 44% for IQ, partial response rate with 5-FU was 31% and the no response rate with IQ was 56%.

Patients should be monitored closely after using topical agents because there is some evidence that exposure might increase the risk of local melanoma.[23] Exposure can also lead to vitiligo or vitiligo-like hypopigmentation[24-26] which might be associated with the development of local or distant autoimmune disorders.[27,28] Autoimmune disorders were not frequently observed after use of topical agents by transplant recipients on immunosuppression.[29-32] It is important to note that topical treatment is ineffective for more advanced stages of penile cancer[33] and, therefore, early and accurate diagnosis is critical before prescribing topical chemotherapy.

LASER THERAPY

Laser therapy can be performed as monotherapy or in conjunction with local margin excision. According to current guidelines a margin of 5 mm is considered oncologically safe.[14, 34, 35] However, multiple recent studies indicate that even tighter margins can be safe and are not associated with worse overall survival. As with all organ sparing techniques, appropriate patient selection for laser therapy is key to maximizing its efficacy.[36] The 4 commonly used lasers are CO_2, argon, potassium titanyl phosphate and YAG.[37-45] The CO_2 and YAG lasers are used most frequently for penile cancer (see Appendix). However, the superficial depth of penetration (limited to 0.1 mm) of the CO_2 laser makes it a suboptimal choice. Microsurgery involves tumor resection with laser by incising lateral and deep margins, followed by peripheral vaporization of the wound to promote collagen formation.[46-48]

The efficacy of CO_2 laser treatment for early stage penile squamous cell carcinoma and carcinoma in situ was assessed in a study of 224 patients.[37] The retrospective analysis excluded cases of pretreated or recurrent lesions, urethral extensions beyond the meatus, regional lymph node involvement and previous concomitant occurrence of other malignancies. Forty patients received reductive systemic chemotherapy with vincristine, bleomycin and methotrexate followed by CO_2 laser tumor excision. The remaining patients were treated with tumor excision using CO_2 laser and no chemotherapy. The technical success rate was approximately 97% with no intraoperative complications and only negligible postoperative complications that ranged from local edema to mild bleeding. The 10-year recurrence rate was 17.5% (95% CI 16.4-18.6) and only 9 patients (5.5%, 95% CI 5.2-5.7) required penile amputation in the 10-year period. Given that this was a retrospective analysis, the decision to administer neoadjuvant chemotherapy was not standardized and likely depended on case specific clinical decision making. Thus, a clear conclusion regarding the efficacy of neoadjuvant chemotherapy before laser treatment cannot be drawn based on this study.

In a study on the histopathological nature of the tumor and correlations with local recurrence Colecchia et al examined 56 cases after CO_2 laser therapy with a median follow-up of 66 months.[38] Among these patients 3 (5.3%) died of unrelated causes, 13 (23.2%) had local tumor recurrence and 4 (7.1%) experienced multiple recurrences with only 1 (1.8%) patient requiring amputation. A strong correlation between histopathology (margin status, depth of invasion, extent of tumor extension) and local recurrence was confirmed.

The YAG laser has an increased depth of penetration (up to 6 mm), and cell death is caused by high wavelength laser beams followed by coagulation of the affected area.[44, 49] Results from newer series on the Nd:YAG laser have been more encouraging compared to those for the CO_2 laser. The efficacy of the Tm:YAG laser for early stage penile cancer was assessed in 26 patients, of whom 11 (47.8%) presented with pTis and 7 with pT1a (30.4%) disease.[44] Invasive cancer recurred postoperatively in 2 cases after a mean follow-up of 6.5 months (IQR 4 to 8). The recurrences were histopathologically classified as grade 3 and were re-treated with Tm:YAG laser. At 12-month follow-up both patients were disease-free. In another retrospective study the efficacy of the Nd:YAG laser was assessed in 32 patients, of whom 25 had stage T1 disease.[49] At a median follow-up of 70 months (range 6 to 120) there were no reported recurrences in any patient with pT1 disease and no significant postoperative limitations in sexual function or micturition.

In a systematic review Maranda et al pooled data from 8 studies to evaluate the efficacy of CO_2 and YAG laser, and photodynamic therapy as first line treatment of Erythroplasia of Queyrat.[50] The CO_2 laser was used in 27 cases and the YAG laser in 7. One patient who underwent Mohs micrographic surgery and CO_2 laser therapy experienced recurrence 4 years after therapy. Treatment was administered in 1 to 3 sessions and follow-up ranged from 4 weeks to 6 months. Complete remission was reported in 33 of the 34 cases (97%).

PDT has been used to treat basal cell carcinomas, squamous cell carcinoma and other skin cancers. Use of a photosensitizer, such as 5-aminolevulinic acid or 5-methyl-aminolevulinic acid, causes accumulation of protoporphyrin IX in tumor cells, which is subsequently activated by visible light and causes selective destruction of abnormal cells. A wide range of treatment durations and hybrid outcomes has been described, generating uncertainty regarding the efficacy of PDT. However, Maranda et al found that use of methyl-aminolevulinic acid as a sensitizer was slightly more effective than aminolevulinic acid as monotherapy, with a 62.5% remission rate for MAL-PDT vs 58.3% for ALA-PDT. The majority of patients maintain an active sexual life after laser therapy with preserved erectile function[37] and no significant sexual dysfunction.[51]

The high rate of local recurrence after laser therapy, which is 48% in some studies,[41, 52, 53] remains a primary limitation of its use. However, the majority of reported recurrences were higher stage penile cancer, emphasizing the importance of carefully assessing the stage and histopathology of the tumor before proceeding with laser as first line treatment. The majority of local recurrences develop within 6 months after laser therapy, beyond which the rate of recurrence rapidly declines to only

2% after 4 years.[54] To improve outcomes from laser surgery, some have argued for the concomitant use of fluorescence guidance,[55] or neoadjuvant/adjuvant radiotherapy or chemotherapy.[37-39] However, more data are required to clearly elucidate the role of these additional treatments in combination with laser therapy.

SURGERY

Because there is no level I evidence guiding treatment of penile cancer, current management guidelines are largely based on retrospective studies. Most experts consider R0 surgical excision of the penile tumor to be the gold standard of treatment. While for higher stage/grade tumors this would mean partial or total penectomy, there has been a shift towards organ preserving techniques for patients with low volume disease of favorable histopathology (stages Tis, Ta, T1 and grades 1, 2). The 4 commonly used surgical approaches for the treatment of early stage penile cancer are 1) organ and sexual function preservation including circumcision, 2) tumor-only excision, 3) Mohs surgery and 4) glansectomy for tumors on the glans penis. More aggressive surgical approaches such as partial and total penectomy are acceptable options for patients with unfavorable histopathology or recurrent disease, or those who would not be surgical candidates in the event of recurrence.

Foreskin circumcision is indicated for preputial disease in uncircumcised men and for acquired phimosis secondary to preputial tumors, and can be curative for low grade and low stage disease.[56, 57] However, close postoperative follow-up is crucial. Higher rates of recurrence have been reported in patients treated with circumcision, especially those with tumors located more proximal and closer to the coronal sulcus. In such cases the circumcision margin will need to be extended to ensure adequate oncologic resection. Similarly, close follow-up is critical for patients with moderately or poorly differentiated tumors (grades 2 and 3), as these will require inguinal node dissection.[56, 57]

Mohs surgery is not widely performed by urologists and to date only 2 retrospective studies of outcomes have been published.[58, 59] The procedure involves sequential excision of tissue layers with concurrent microscopic examination of the undersurface of each layer to ensure negative margins. The aim of this approach is to achieve negative margins while maximally sparing tissues uninvolved by tumorous growth. Mohs surgery can be considered for disease of favorable histopathology and when the affected area is within the distal penis or glans penis.[60] In the original series Mohs surgery efficacy was based on Jackson stage.[58] In 29 patients with Jackson stage I or II disease the 5-year recurrence-free survival rate was 79.3%. Shindel et al reported results of their retrospective study of 33 patients with stage Tis (26), T1 (4), T2 (7) and T3 (4) penile cancer.[59] Five procedures were terminated with positive margins because of urethral involvement in 3 and defect size in 2.

Follow-up data were available for 25 patients, of whom 8 (32%) had recurrence, which was managed by repeat Mohs micrographic surgery in 7 and penectomy in 1. Tumor progressed from T1 to T3 (meatal involvement) in 1 case and from T1 to inguinal lymph node involvement in 1 case. One patient died of metastatic disease. At a mean follow-up of almost 5 years the recurrence-free survival rate was 68%, overall survival was 92% and disease specific survival was 96%. Currently there is no evidence to suggest Mohs surgery is superior to negative intraoperative frozen section margins in terms of oncologic outcomes.

Total and partial glansectomy, and glans resurfacing have gained interest since nearly 80% of penile squamous cell carcinoma occurs distally,[57, 61] with the majority (48%) of lesions developing on the glans penis (figs. 1 to 3).[2, 62] However, this surgical approach can result in significant side effects including wound contraction and growth of the skin graft over or around the urethral meatus.[53, 55, 63] Further postoperative assessment of functional and sexual outcomes is required,[64] as even after successful surgical resection, cancer specific survival rates are dependent on tumor pattern of invasion and stage. Tumors of an infiltrating pattern and/or higher stage are strongly correlated with a decrease in survival.[65] More frequent follow-up is recommended for these higher risk cases to assess for local recurrence, especially when 2 or more risk factors are present.[66]

In experienced hands tumor excision with negative intraoperative frozen section margins can be performed safely in well selected patients. In light of more evidence, the previous goal of a 2 cm surgical margin is no longer applicable. Histological analysis of 64 penectomy specimens by Agrawal et al confirmed that microscopic tumor spread is highly correlated with tumor grade.[67] The maximum proximal histological extent was 5 mm for grade 1 and 2 tumors and 10 mm for grade 3 tumors. In another study higher tumor grade correlated with a greater likelihood of disease recurrence following penile preserving surgery.[35] There was no recurrence in 9 of 88 patients with T1 tumors and histopathological grade 1, 1 of 19 with histopathological grade 2 and 5 of 60 with histopathological grade 3 disease.

In a retrospective study based on tumor stage the 5-year recurrence-free survival rates following penile sparing surgery were 75% for stage Ta/Tis disease, 71.4% for stage T1 disease and an overall rate of 88.1%.[68] Moreover, positive margins were associated with a higher rate of recurrence on multivariate analysis but this did not correlate with disease stage. The rate of positive margins ranged from 28.7% for T2 tumors to 30.9% and 35.9% for Ta/Tis and T1 tumors, respectively (p=0.214). Recurrences developed in the first year in 39.1% of the cases.

Overall, penile preserving techniques are feasible options and should be considered for low volume, low stage penile cancer with favorable histopathology. The choice of therapy should involve a shared decision making process between the patient and the surgeon highlighting the risks and benefits of each approach. Close follow-up for at least 5 years is required to detect and re-treat any potential recurrences.

RADIATION

Traditionally, radiation therapy via external beams or radiation emitting implants was promoted as an efficient approach to early stage penile cancers. The American Brachytherapy Society and European Society of Therapeutic Radiation Oncology reported outcomes of brachytherapy primarily focused on stages T1 and T2 disease.[69-73] A recent study concluded that radiotherapy was associated with more local complications and lower control rates.[45] Possible complications include urethral stricture, glans necrosis and late onset fibrosis of the corpora cavernosa.[70, 73, 74] Urologists may consider radiation for patients who are unfit for surgery and are willing to accept the late onset side effects associated with it. Given the higher success rates of surgical approaches, surgery remains the preferred approach to

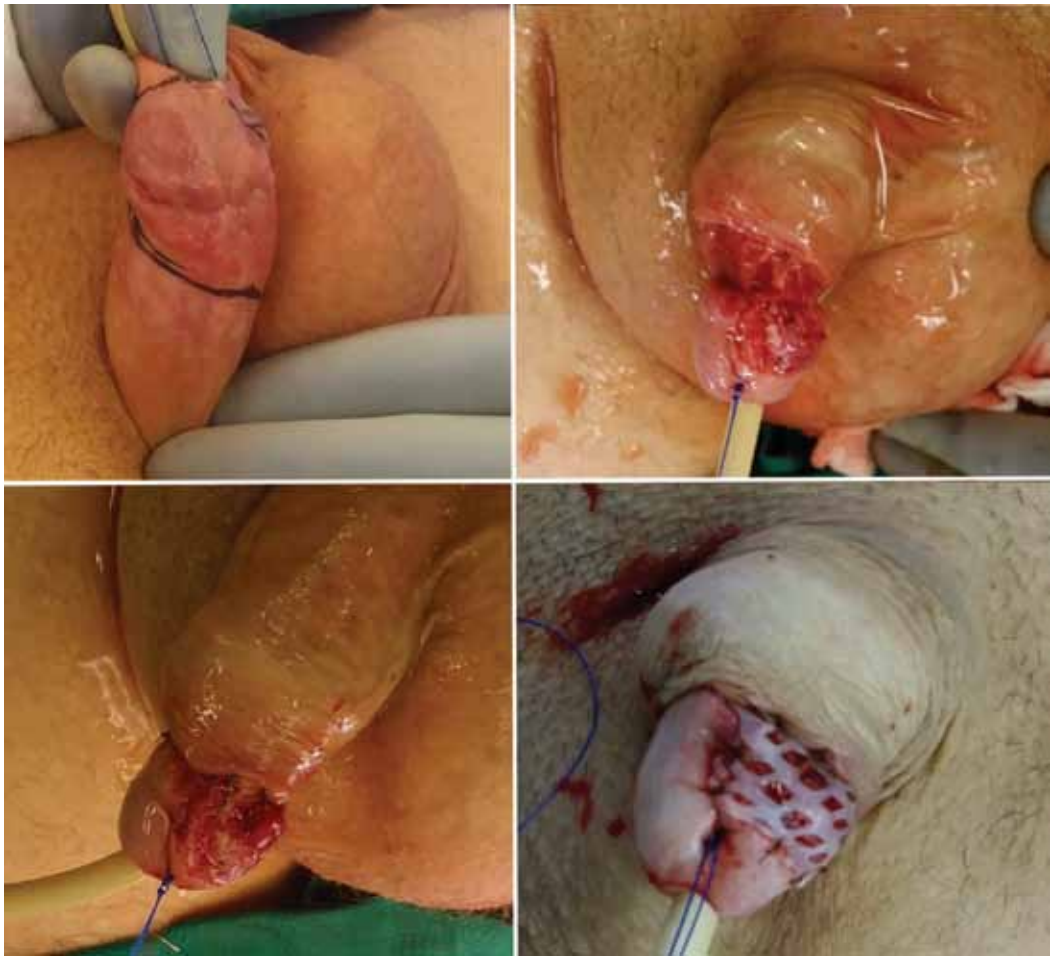

Figure 1. Partial glansectomy with concomitant partial thickness skin grafting.

Figure 2. Glans resurfacing with concomitant partial thickness skin grafting.

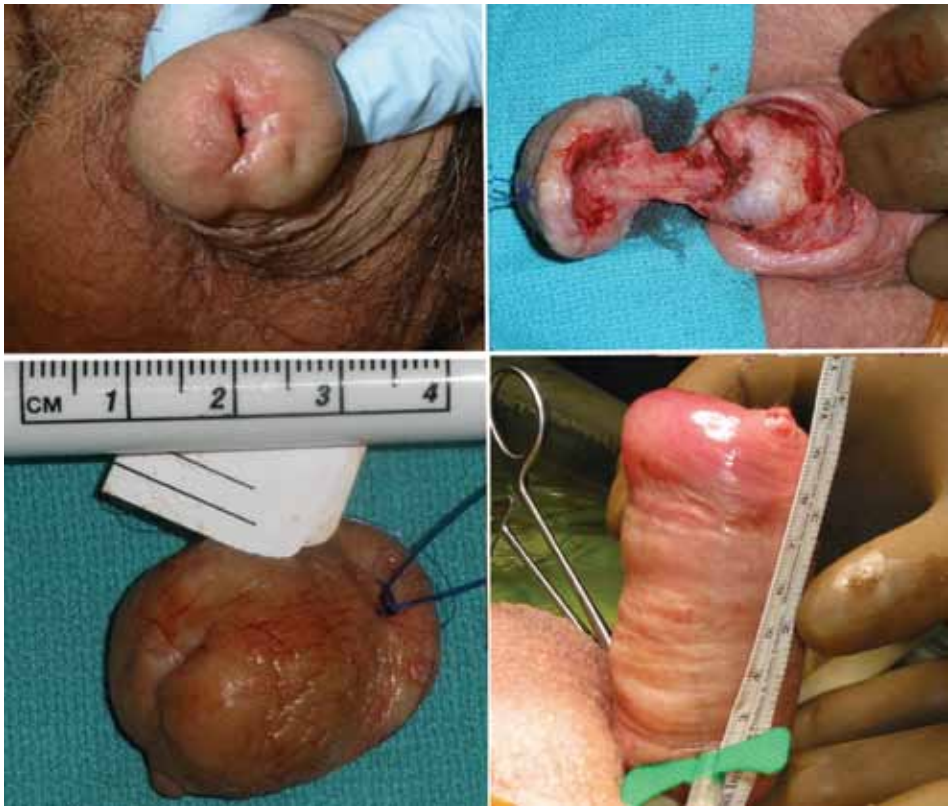

Figure 3. Total glansectomy.

penile cancer, and should be performed with the patient under light sedation with a penile block for early stage tumors (fig. 4).

CONCLUSION

Organ preserving approaches are safe and feasible for early stage, low grade squamous cell carcinoma of the penis. Accurate pathological diagnosis is necessary before initiating therapy, and inguinal lymph nodes must be evaluated for lymphadenopathy. Topical therapies with 5-FU and IQ are safe for non-bulky tumors, whereas bulkier tumors that do not respond to topical therapy can be managed with laser therapy and surgical excision (excisional biopsy, circumcision, glans resurfacing, partial and total glansectomy).

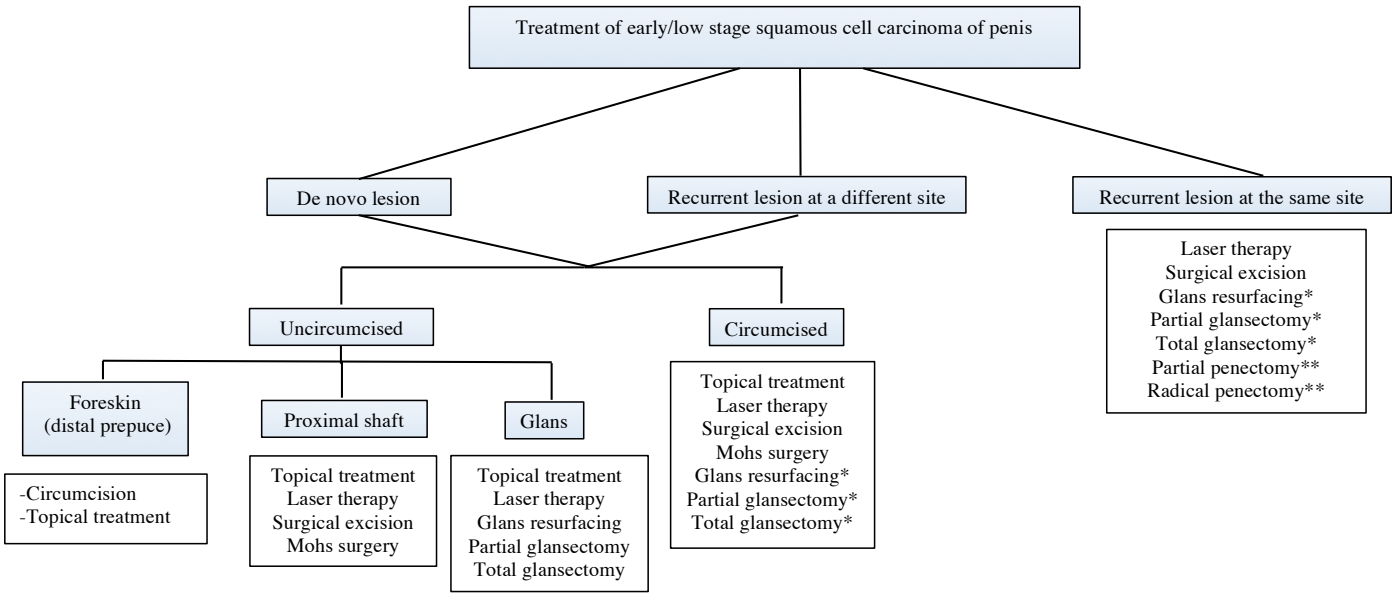

Figure 4. Treatment algorithm for early/low stage penile squamous cell carcinoma. Asterisk indicates lesions located on glans penis. Double asterisks indicate partial or radical penectomy reserved for high risk of recurrent lesions in cases in which follow-up after treatment with other possible organ preserving approaches is unreliable.

DID YOU KNOW?

- Topical treatments, cryotherapy, circumcision, laser treatment and photodynamic therapy can be considered first line treatment options for non-invasive and early stage penile malignancies (carcinoma in situ, Ta and T1).
- It is important to note that topical treatment is ineffective for more advanced stages of penile cancer and, therefore, early and accurate diagnosis is critical prior to prescribing topical chemotherapy.
- Laser therapy can lead to good cosmesis and function. However, the high rate of local recurrence remains a primary limitation to this mode of treatment. The majority of local recurrences develop within the first 6 months after laser therapy. Therefore, close follow-up especially during the first 6 months is recommended.
- The 4 commonly performed surgical approaches for treatment of early stage penile cancer (Tis, Ta, T1, and grades 1 and 2) with a focus on organ and sexual function preservation are circumcision, tumor only excision, Mohs surgery and glansectomy for tumors on the glans penis. Regardless of the surgical approach, the goal should be to obtain R0 resection with negative margins.
- More aggressive surgical approaches such as partial and total penectomy are acceptable options for unfavorable histopathology or recurrent disease, or patients who would not be surgical candidates in the event of recurrence.

Appendix. Different laser modalities used for treatment of early stage penile cancer

Type	Characteristics	Technique	Follow-up	Recovery	Indications
Carbon dioxide laser	• Most commonly used. • Superficial depth of penetration limited to 0.1 mm. • Continuous wave and super-pulsed wave modest at recommended setting of 15-20 W.	1. Acetic acid preparation can make visualization of lesions more accurate and should be considered. 2. Most commonly, vaporization of the lesion, defocused beam at peripheral distance of 3-5 mm and continue to the reach depth of 0.5 mm at the wound bed. 3. Laser resection possible by incising lateral and deep margin. 4. Incision depth shall be 2.5 mm within lamina propria and 5 mm from visible tumor border.	Post-procedural follow-up after 2 months, then every 3 months for the first 3 years, and biannually thereafter.	Typically within 6 weeks.	1. Lesions less than 20 mm. in diameter. 2. Superficial tumors with shallow depth usually 1-2 mm. 3. Photodynamic control in conjunction with CO_2 laser is possible, but rarely used. 4. Multimodality therapy with adjuvant or neo-adjuvant radiotherapy possible, but very rarely indicated. 5. Even more rarely, and not practiced this way in the USA, multimodality therapy with adjuvant or neo-adjuvant chemotherapy in cupuliform, papillomatous warty like with plurifocal exophytic lesions +/- ulcers or lesions > 20 mm. in size.
Nd:YAG laser	• Deeper depth of penetration. • Wavelength 1064 nm. • Power and energy is adjustable with continuous wave mode at 30-50 W.	1. Examining and mapping with 5% acetic acid for 20 min. 2. Local and continuous-wave mode at 30–50 W of console power in air (wave length: 1064 nm). 3. Intermittent cooling by locally administered saline, especially cold saline solution. 4. Visualization improved by photodynamic diagnosis.	Post-procedural follow-up every 3 months for the first 2 years, biannually thereafter.	Typically within 2 months.	1. Tumors up to 6 mm. in size. 2. Sizeable and deeper tumors. 3. Multimodality therapy with adjuvant or neo-adjuvant brachytherapy.

continued

Appendix, *continued*

Argon laser	Wavelength 488-514 nm.	1. Argon laser targets photosensitive agents (chromophobes) that are administered within the skin lesion. 2. Tumor cells absorb the agent more than surrounding tissue. 3. Argon laser, subsequently, activates the medicated area that destroys the tumor cells.	Within 1 week, then 2 months of treatment. Every 3 months thereafter.	Can take as long as 6-8 weeks.	Unlike Nd:YAG and carbon dioxide lasers, argon laser shall be restricted to macular, popular and pigmented lesions.
Potassium titanyl phosphate laser (KTP/532)	• Wavelength 532 nm. • Power setting at 10 to 15 W.	Potassium-titanyl-phosphate (KTP/532) laser is delivered at a power setting of 10 to 15 W.	Initially at 3-month and later at 6- to 12-month intervals.	Can take up to 2 months.	Not used frequently anymore.

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Study Questions Volume 39 Lesson 8

1. A 59-year-old active smoker with a history of pTa squamous cell carcinoma of the distal penile shaft previously treated with laser ablation presents with a 2 cm lesion near the edge of the site of the previous lesion. Which option is recommended to achieve optimum oncologic outcome?
   a. Local chemotherapy with imiquimod
   b. Repeat laser ablation
   c. Surgical excision
   d. Radiotherapy

2. In patients with low volume, favorable histopathology penile cancer who wish to proceed with organ preserving surgery the highest rate of recurrence is seen with
   a. surgical excision with a 2 cm negative margin
   b. surgical excision with a 1 cm negative margin
   c. laser therapy
   d. Mohs surgery

3. A 55-year-old man presents with a 5 mm raised erythematous lesion on the glans penis. Imaging is negative for lymphadenopathy. The next step is
   a. surveillance
   b. prescribe 5-fluorouracil
   c. surgical excision of the lesion
   d. partial or radical penectomy

4. A major drawback of the CO_2 laser for treating penile cancer is that it
   a. requires photosensitizing agents
   b. causes tissue necrosis and organ loss
   c. is associated with systemic autoimmune disorders
   d. has a superficial depth of penetration and high rate of recurrence

5. The most acceptable treatment strategy for a 50-year-old uncircumcised man with a non-invasive 5 cm penile cancer (Tis) involving the coronal sulcus is
   a. Mohs surgery
   b. laser therapy followed by 5 mm local margin excision
   c. topical application of 5% imiquimod and 5-fluorouracil cream
   d. circumcision followed by tumor excision with a 5 mm oncologic safety margin with regular follow-up

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