

DISEASE MANAGEMENT OF THE PRIMARY TUMOUR:

The aims of the treatment of the primary tumour are complete tumour removal with as much organ preservation as possible, without compromising oncological control. **Histological diagnosis and local staging must be obtained before non-surgical treatments can be considered.**

Treatment of superficial non-invasive disease (PeIN, Ta)

Penile intra-epithelial neoplasia can progress to invasive lesions in 2.6–13% of patients, despite treatment. **Definitive eradication and diligent follow-up monitoring are important.** Most PeIN lesions are located on the mucosal surfaces of the glans or prepuce whilst lichen sclerosis also affects the prepuce and circumcision should be the primary surgical option.

- **Topical therapies:** Topical therapy with imiquimod (IQ) or 5-fluorouracil (5-FU) are effective non-invasive first-line treatment options. Response and recurrence rates are 40–100% and 20% for IQ and 48–74% and 11% for 5-FU.
- **Laser ablation:** Response rates are 52–100% and recurrence rates 7–48%.
- **Surgery:** Extensive PeIN, residual PeIN in resection margins or recurrent disease after ablative or topical therapy, can be treated by surgical excision. **Glans resurfacing** consists of full thickness removal of the glandular epithelium followed by reconstruction with a graft. Recurrence rates are reported to be low (0–20%) and cosmesis is acceptable.

Treatment of invasive disease confined to the glans (cT1/T2)

When feasible, small and localised invasive lesions should receive organ-sparing treatment.

A systematic review (SR) including retrospective studies on organ-sparing surgical treatment of the primary lesion shows that cumulative mean 5-year recurrence-free rates (RFRs) are 76.7–82%. For (partial) amputative surgery these are 83.9–93.3%.

- **Width of negative surgical margins:** Tumour distance to the resection margin < 1 mm resulted in higher local recurrence rates in a recent large retrospective case series from a tertiary referral centre.
- **Laser ablation:** In line with results achieved in non-invasive and superficially-invasive penile lesions, it has been proposed as an option for smaller invasive lesions. The cumulative mean 5-year RFR was 69.4%.
- **Moh's micrographic surgery:** is a surgical technique by which tissue is excised and processed with en face histological margins in real time to give a complete circumferential and deep margin. It aims at maximal organ preservation by adopting margin-guided excision. As data are very limited, it is not routinely recommended.
- **Wide local excision and circumcision:** For small, distal preputial penile cancer, circumcision alone usually presents adequate treatment. However, lesions located on the corona or glans, limited in size, may be treated with wide local excision which should include a margin of clinically normal-appearing skin around the tumour and surrounding erythema.
- **Glans resurfacing:** Besides its established effects in the therapy of PeIN, total or partial glans resurfacing has been reported to be employed for superficially-invasive lesions combined with deeper resection at the site of invasion. Recurrence rates are as low as 4%.
- **Glansectomy and partial penectomy:** Patients with tumours confined to the glans and prepuce that are not eligible for wide local excision or glans resurfacing are good candidates for glansectomy. Amputative and partial amputative surgery is reserved for more advanced disease.
- **Radiotherapy for T1 and T2 disease:** The cumulative mean 5-year RFRs are 78.6% after brachytherapy and 55.2% after external radiotherapy.

Locally advanced disease (T3–T4)

- **Resectable disease:** For cT3 patients with obvious involvement of the corpora cavernosa, **partial amputation** is standard. Patients can be offered reconstructive options such as urethral centralisation and/or neo-glans formation with the use of a graft. Two studies in higher-risk patients treated with radical glansectomy or partial penectomy show that local recurrence in these instances is associated with poor survival.

Radical amputation and diversion of urination with a perineal urethrostomy is reserved for those patients in whom a resection with a safe margin would result in the inability to void standing upright or without wetting the scrotum.

Radiotherapy for locally-advanced penile lesions should be undertaken with concurrent chemotherapy. In case of locally-advanced and ulcerated cases which are resectable, composite myocutaneous flaps or advancement flaps may be needed to cover the surgical defect.

- **Non-resectable disease:** In non-resectable disease, induction chemotherapy offers the ability to downstage disease and thereby enable surgical resection among responders, even among men with advanced penile cancer. Although there is considerable heterogeneity in the regimens and cohorts combining advanced nodal disease and unresectable primary tumours, objective responses are observed in 29–60% of patients

Recommendations	Strength rating
Offer a balanced and individualised discussion on benefits and harms of possible treatments options with the goal of shared decision making.	Strong
Inform patients of the higher risk of local recurrence when using organ-sparing treatments compared to amputative surgery.	Strong

Topical therapy	
Offer topical therapy with 5-fluorouracil or imiquimod to patients with biopsy-confirmed penile intra-epithelial neoplasia (PeIN).	Weak
Clinically assess treatment effects after a treatment-free interval and in cases of doubt perform a biopsy. If topical treatment fails, it should not be repeated.	Weak
Laser ablation	
Offer laser ablation using CO ₂ or Nd:YAG laser to patients with biopsy-confirmed PeIN, Ta or T1 lesions.	Weak

Organ-sparing treatment: surgery (circumcision, wide local excision, glansectomy and glans resurfacing)	
Offer organ-sparing surgery and reconstructive techniques to patients with lesions confined to the glans and prepuce (PeIN, Ta, T1–T2) and who are willing to comply with strict follow-up.	Strong
Perform intra-operative frozen section analysis of resection margins in cases of doubt on the completeness of resection.	Weak
Offer salvage organ-sparing surgery to patients with small recurrences not involving the corpora cavernosa.	Weak

Organ-sparing treatment: radiotherapy (EBRT and brachytherapy)	
Offer radiotherapy to selected patients with biopsy-confirmed T1 or T2 lesions.	Strong

Amputative surgery (partial- and total penectomy)	
Offer partial penectomy, with or without reconstruction, to patients with invasion of the corpora cavernosa (T3) and those not willing to undergo organ-sparing surgery or not willing to comply with strict follow-up.	Strong
Offer total penectomy with perineal urethrostomy to patients with large invasive tumours not amenable to partial amputation.	Strong
Offer amputative surgery to patients with large local recurrences or corpora cavernosa involvement.	Weak

Multimodal therapy	
Offer induction chemotherapy followed by surgery to responders, or chemo-radiotherapy to patients with non-resectable advanced primary lesions, or to patients with locally advanced-disease who refuse surgical management.	Weak