

Regional lymph node management: clinically evident disease (cN1–cN3)

Lymphatic metastases in penile cancer follow a predictable drainage pattern from the superficial and deep inguinal lymph nodes (LNs) to the ipsilateral pelvic LNs, with no direct spread to the pelvis or inferior groin regions. Sentinel nodes (SN) are mainly in the medial superior and central inguinal zones, and crossover metastases to the contralateral pelvis are rare. Further spread to retroperitoneal nodes is considered systemic disease.

Regional LN management is crucial for prognosis, as nodal involvement is the most significant predictor of survival. Radical lymph node dissection (LND) is the preferred treatment for limited disease, while multimodal approaches (surgery, chemotherapy, radiotherapy) are required for advanced cases. Clinically positive LNs (cN1/cN2) require surgical assessment, while fixed inguinal LNs (cN3) or pelvic metastases demand induction chemotherapy followed by surgery. Extra-capsular extension (ENE) or pelvic LN metastases (pN3) indicate a high risk of progression, necessitating multimodal treatment.

cN1–N2 disease: radical inguinal lymph node dissection (rILND)

Indication for rILND: rILND remains the standard of care for cN1–N2 disease and cN0 patients with a tumor-positive SN. In low-volume disease (pN1), it is curative with outcomes comparable to those without nodal disease. However, studies show non-adherence to guidelines, affecting overall survival (OS).

Definition & Variability: Daseler’s 1948 classical description of rILND is widely referenced, but variability exists in high-volume centers. A modified fascial-sparing ILND (fsILND) has demonstrated comparable oncologic outcomes, but no direct comparison to rILND exists.

Lymph Node Yield & Density: Studies associate LNY/LNDen with survival, but variability in surgical templates and pathological assessment limits their use as standard predictors.

Timing of Surgery: Early ILND within six weeks of primary surgery shows better survival compared to delayed ILND. However, in pN1–2 disease, evidence regarding optimal timing remains limited, with some studies showing no significant benefit of early vs. late dissection.

Complications: rILND has significant morbidity (21–55%), including wound infections (2–43%), lymphoedema (3.1–30%), lymphocele (1.8–26%), and seroma (2.4–60%). Despite this, it is lifesaving and should not be avoided.

Minimally-Invasive Approaches: Video-endoscopic Inguinal Lymphadenectomy (VEIL) and robot-assisted VEIL (RAVEIL) have been introduced to reduce morbidity, showing similar LN yields, shorter hospital stays, and lower wound complications, but equivalent lymphocele and readmission rates. Follow-up remains short, and most cases involved prophylactic rather than therapeutic procedures, limiting their role in current guidelines.

Recommendations	Strength rating
In patients with cN1 disease offer either ipsilateral: <ul style="list-style-type: none"> fascial-sparing inguinal lymph node dissection (ILND) open radical ILND; sparing the saphenous vein, if possible 	Strong
In patients with cN2 disease offer ipsilateral open radical ILND; sparing the saphenous vein, if possible.	Strong
Offer minimally-invasive ILND to patients with cN1–2 disease only as part of a clinical trial.	Strong
Offer neoadjuvant chemotherapy as an alternative approach to upfront surgery to selected patients with bulky mobile inguinal nodes or bilateral disease (cN2) who are candidates for cisplatin and taxane-based chemotherapy (see Section 6.4.1).	Weak
Complete surgical inguinal and pelvic nodal management within three months of diagnosis (unless the patient has undergone prior neoadjuvant chemotherapy).	Weak

Prophylactic pelvic lymph node dissection (pPLND)

Indications and Risk Factors: pPLND is primarily a staging procedure to identify candidates for early adjuvant therapy, though it may provide therapeutic benefit in select cases. Risk factors for pelvic LN metastasis include ≥ 3 positive inguinal LNs (without extracapsular extension), extracapsular spread, strong p53 immunoreactivity, LN density $>30\%$, and high tumor grade.

Extent of Dissection: Studies show external iliac and obturator nodes are the most commonly involved sites. A LN yield >9 has been associated with improved recurrence-free survival (RFS). Crossover metastasis from one inguinal region to the contralateral pelvis, though rare, has been observed.

Survival and Recurrence: The therapeutic benefit of pPLND over surveillance or adjuvant radiotherapy remains controversial. The 5-year disease-specific survival (DSS) for all pPLND patients is 51%, but significantly lower for those with positive pelvic nodes (17% vs. 62%, $p < 0.001$). In N2 disease, 3-year OS was higher with PLND (83.3% vs. 50.2%, $p = 0.03$), though this benefit was not observed in N3 patients.

Complications: Data on complications is limited, but open PLND has an 18% complication rate.

Minimally-Invasive vs. Open PLND: No studies have assessed minimally-invasive pPLND in penile cancer.

Recommendations	Strength rating
Offer open or minimally-invasive prophylactic ipsilateral pelvic lymphadenectomy to patients if: <ul style="list-style-type: none"> three or more inguinal nodes are involved on one side on pathological examination extranodal extension is reported on pathological examination 	Weak
Complete surgical inguinal and pelvic nodal management within three months of diagnosis (unless the patient has undergone neoadjuvant chemotherapy).	Weak

Clinical N3 disease (cN3)

Diagnostic Evaluation: Patients with fixed inguinal masses or pelvic lymphadenopathy (cN3) should undergo cross-sectional imaging (PET/CT or CT) for staging. A biopsy is only required if the penile cancer diagnosis is not previously established.

Management Strategy: Neoadjuvant chemotherapy (NAC) is the preferred approach, with 53% radiological response rates and 12.8% complete pathological response. Surgery is indicated for patients who respond or show no disease progression. Pre-operative radiotherapy has shown limited success, and surgery-first strategies result in high complication rates (65–77%) and poor survival outcomes.

Patient Selection for Surgery: Patients responding to NAC have a 5-year survival of 56.9%. For those ineligible for multi-agent chemotherapy, pre-operative chemo-radiation may be considered, though evidence is weak.

Surgical Technique: ILND should be performed 5–8 weeks post-chemotherapy to allow for recovery. Surgery must include wide resection of involved skin, and minimally invasive techniques are not suitable for cN3 disease. If pelvic LN metastases are present at diagnosis, simultaneous PLND is recommended. In cases of bulky inguinal metastases without clinical pelvic involvement, prophylactic ipsilateral PLND is advised due to high rates of microscopic pelvic disease (44–100%).

Surgical Complications: Major complications include infection/sepsis (1.5–4.5%), lymphocele requiring drainage (0–3.8%), wound dehiscence/necrosis (1.5–5.6%), pneumonia (0–2.9%), thrombosis (0–8.7%), and perioperative death (0–5.6%). Experienced centers report major complications in fewer than 10% of patients.

Recommendations	Strength rating
Offer neoadjuvant chemotherapy (NAC) using a cisplatin- and taxane-based combination to chemotherapy-fit patients with pelvic lymph node involvement or those with extensive inguinal involvement (cN3), in preference to up front surgery. (see Section 6.4.1).	Weak
Offer surgery to patients responding to NAC in whom resection is feasible.	Strong
Offer surgery to patients who have not progressed during NAC, but resection is feasible. See also (chemo)radiation.	Weak
Do not offer Video Endoscopic Inguinal lymphadenectomy.	Strong