Perioperative systemic therapy and radiotherapy in node-positive penile squamous cell carcinoma: Current evidence on neoadjuvant and adjuvant strategies in the InPACT Er

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ABSTRACT

Introduction: Penile squamous cell carcinoma (PSCC) is a rare but aggressive malignancy in which prognosis is largely determined by nodal involvement. In patients with node-positive disease, surgery alone is frequently insufficient, particularly in the presence of bulky inguinal metastases, pelvic nodal disease, or extranodal extension. Perioperative strategies incorporating systemic therapy and/or radiotherapy have therefore become increasingly relevant, although the evidence base remains limited and predominantly non-randomized. We aimed to critically review the available evidence on neoadjuvant chemotherapy (NAC), adjuvant chemotherapy (ACT), adjuvant radiotherapy (ART), and combined chemoradiotherapy in node-positive PSCC and to contextualize current practice within the framework of contemporary international guidelines and the ongoing InPACT trial.
Methods: Narrative review with structured literature search of PubMed/MEDLINE, EMBASE, Scopus, the Cochrane Library, and *ClinicalTrials.gov* covering the 15 years preceding the search date, with a targeted update through 2025. Selected phase 2 immunotherapy studies reported in 2025, including full-text publications and conference presentations (ASCO GU 2025 and ESMO 2025), were additionally included as contextual evidence for emerging perioperative strategies.
Results: Cisplatin/taxane-based NAC remains the best-established perioperative approach for selected cN2–N3 patients, with objective response rates of 50–57% and substantially longer survival in clinical responders than non-responders. Retrospective data suggest that ACT may be associated with improved survival in pN3 disease, while ART appears to contribute to locoregional control in patients with extranodal extension, with retrospective data suggesting that dose intensity may influence in-field control. Immunotherapy-based combinations have produced encouraging early-phase signals but remain preliminary and should not yet be regarded as practice-defining.
Conclusions: Current evidence supports cisplatin/taxane-based NAC as the most established perioperative strategy for chemotherapy-fit patients with cN2–N3 PSCC. ACT may be considered mainly in selected pN3 patients or in those with other high-risk pathological features after lymphadenectomy, whereas ART appears most relevant for locoregional risk reduction, particularly in the presence of inguinal extranodal extension.

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INTRODUCTION

Penile squamous cell carcinoma (PSCC) accounts for an estimated 37,699 new cases and 13,729 deaths annually worldwide (GLOBOCAN 2022), with an age-standardised incidence of 0.8 per 100,000 men globally but representing up to 10% of all male malignancies in parts of sub-Saharan Africa, South America, and South-East Asia [1]. The biological behaviour of PSCC is profoundly shaped by HPV and p53 status. The 2022 WHO classification distinguishes HPV-associated subtypes — predominantly basaloid and warty carcinomas — which confer a more favourable prognosis, from HPV-independent tumours driven by TP53 mutations, which are more aggressive and relatively resistant to systemic therapy and irradiation [2]. The surrogate marker p16 immunohistochemistry yields five-year disease-specific survival (DSS) of approximately 88% in p16-positive versus 58% in p16-negative tumours [2]. High co-expression of PD-L1 (40–60% of cases) and EGFR (>90% of cases) provides the biological substrate for emerging immunotherapy and targeted therapy combinations [2,3].

Lymph node status remains the single most powerful prognostic determinant in PSCC. Five-year cancer-specific survival (CSS) declines substantially across nodal stages — from over 90% in pN0 to approximately 10–33% in pN3 disease — with extranodal extension (ENE) and pelvic nodal involvement representing the most adverse pathological features [4]. This stepwise lymphatic dissemination, from superficial inguinal to deep inguinal and pelvic nodes, defines the therapeutic landscape and the rationale for perioperative treatment intensification.

The main perioperative approaches include NAC, postoperative systemic therapy, postoperative radiotherapy, and, in selected settings, combined chemoradiotherapy. NAC to downstage bulky or fixed nodal disease before consolidative surgery; ACT and/or ART to eradicate micrometastatic disease and improve locoregional control after lymphadenectomy; and combined adjuvant chemoradiotherapy (ACRT). More recently, immune checkpoint inhibitors have entered the field, initially in advanced disease, and have generated interest in earlier perioperative integration. The 2023 EAU–ASCO Collaborative Guidelines endorse cisplatin/taxane-based NAC for cN2–N3 patients and recommend discussion of ACT and ART for pN2–N3 patients after lymphadenectomy — both as weak recommendations reflecting the absence of randomised evidence [4]. The InPACT trial (NCT02305654/EA8134) was specifically designed to address this fundamental evidence gap [5,24].

The purpose of this review is to critically examine the strength and limitations of the current evidence on perioperative systemic therapy and radiotherapy in node-positive PSCC, distinguishing evidence derived from strictly perioperative populations from data extrapolated from advanced disease settings. Selected advanced/metastatic immunotherapy studies were included strictly as contextual, hypothesis-generating evidence and not as proof of perioperative efficacy.

METHODS

This article was designed as a narrative review with a structured literature search. PubMed/MEDLINE, EMBASE, Scopus, the Cochrane Library, and ClinicalTrials.gov were searched for studies published within the 15 years preceding the search date. Search terms combined: penile neoplasms, penile squamous cell carcinoma, PSCC, neoadjuvant chemotherapy, adjuvant chemotherapy, adjuvant radiotherapy, chemoradiotherapy, perioperative therapy, TIP, TPF, immunotherapy, pembrolizumab, and InPACT. Reference lists of key reviews, guidelines, and identified articles were manually checked for additional relevant studies.

Eligible studies reported at least one of the following oncological outcomes: objective response rate (ORR), pathological complete response (pCR), overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS), or recurrence-free survival (RFS), in histologically confirmed node-positive PSCC receiving perioperative systemic therapy or radiotherapy, with a minimum of ten patients. Case reports, series of fewer than ten patients, and studies focused exclusively on primary tumour treatment without nodal outcome data were excluded.

Retrieved records were screened by title and abstract, followed by full-text review of potentially relevant articles. Thirteen studies formed the core perioperative evidence base summarised in Supplementary Table 1 (available at *cuaj.ca*); additional retrospective and contextual studies were incorporated selectively to inform the broader narrative synthesis. Supplementary Table 1 (available

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at *cuaj.ca*) summarises the studies specifically informing perioperative management, whereas advanced/metastatic immunotherapy studies are discussed separately as contextual evidence.

Given the rarity of the disease and the scarcity of dedicated perioperative data, selected phase II immunotherapy studies reported in 2025, including full-text publications and congress presentations at ASCO GU 2025 and ESMO 2025 [21–23], were additionally incorporated when they provided biologically relevant context or early efficacy signals applicable to the perioperative setting. These studies are explicitly identified as advanced/metastatic disease evidence throughout the text and in Supplementary Table 1 (available at *cuaj.ca*), and were not used to draw conclusions about perioperative efficacy.

This review was not designed as a formal systematic review or meta-analysis. No quantitative data pooling, PRISMA flow diagram, or validated risk-of-bias instrument was applied. Evidence quality was appraised narratively according to study design, sample size, endpoint consistency, and risk of confounding. The 2023 EAU–ASCO Collaborative Guidelines served as the principal interpretative framework [4], complemented by NCCN v2.2025 and ESMO-EURACAN 2024 recommendations.

RESULTS & DISCUSSION

Surgical foundation and rationale for perioperative intensification

Radical inguinal lymph node dissection (ILND) remains the cornerstone of potentially curative treatment in node-positive PSCC. Minimally invasive approaches — video-endoscopic (VEILND) and robot-assisted — have substantially reduced the morbidity profile while maintaining oncological equivalence in pN1–N2 disease [4]. Following ILND, approximately 31.9% of patients experience recurrence, with the vast majority occurring within 48 months: median time to inguinal recurrence is 12 months, and to distant metastasis 10 months [4]. This rapid recurrence kinetics provides the principal biological argument for early perioperative systemic intervention, as the window for effective eradication of micrometastatic disease narrows substantially with delay. However, surgery alone may be curative in patients with limited nodal burden, and the decision to intensify with perioperative therapy must be balanced against treatment toxicity, particularly in a population that frequently presents with significant comorbidities.

Neoadjuvant chemotherapy: The most established perioperative approach

Among available perioperative strategies, NAC has the most consistent clinical rationale, particularly in cN2–N3 disease when nodal bulk or fixation raises concerns regarding resectability. The TIP regimen (paclitaxel 175 mg/m², ifosfamide 1.2 g/m² days 1–3, cisplatin 25 mg/m² days 1–3, every 21 days for 4 cycles) represents the historical reference, established by Pagliaro et al. in a prospective phase II trial of 30 cN2–N3 patients: ORR 50%, pCR 10%, median OS 17.1 months, with long-term disease-free survival in 67% of surgical responders [6]. These findings established platinum-taxane-based therapy as the most credible conventional perioperative platform. TPF-based regimens (docetaxel/cisplatin/5-FU) yielded comparable ORR (38–44%) but lower pCR rates (4–14%) and greater haematological toxicity in two subsequent prospective phase II trials [7,8], contributing to the continued clinical preference for TIP over TPF, though no randomised head-to-head comparison exists.

The largest real-world evidence base comes from Rose et al. (JNCI, 2024), a retrospective international multicentre cohort of 209 patients with locally advanced, clinically node-positive PSCC treated with NAC followed by consolidative lymphadenectomy across 11 institutions in North America, South America, and Europe [9]. TIP was administered in 73% of patients. ORR by RECIST 1.1 was 57.2% (43.2% partial response, 13.9% complete response), with a pathological lymph node complete response (ypN0) rate of 24.8%. The central finding was a profound survival differential between responders and non-responders: median OS 73.0 months versus 17.0 months ($p<0.01$), and median PFS 50.0 versus 11.0 months ($p<0.01$) [9]. On multivariable analysis, objective response, ypN status, and neutrophil-to-lymphocyte ratio were independently associated with OS [9]. A meta-analysis by Azizi et al. (2020; n=182 across 10 studies) confirmed a pooled ORR of 53% (95% CI: 42–64%), with taxane-platinum regimens yielding numerically higher response rates [10].

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These results support NAC as a reasonable and guideline-concordant strategy in selected cN2–N3 patients. However, given the retrospective nature of the Rose et al. data and the inherent responder-versus-non-responder selection bias — in which response to treatment functions simultaneously as a treatment effect and a surrogate of tumour biology — the magnitude of benefit should be interpreted with appropriate caution. Despite guideline endorsement, NAC is administered to only approximately 10% of eligible cN2–N3 patients in real-world practice [4].

Adjuvant chemotherapy: Plausible but supported mainly by retrospective evidence

The rationale for ACT is strongest in patients with high-risk pathological features after lymphadenectomy, particularly multiple positive nodes, pelvic nodal involvement, or ENE. The most cited retrospective evidence comes from Sharma et al. (2015), a multicentre study of 84 patients with pN3 PSCC across four international institutions [11]. ACT (cisplatin-based) was independently associated with improved OS on multivariable analysis (median OS 21.7 vs. 10.1 months; HR 0.40; 95% CI 0.19–0.87; p=0.021). However, important imbalances between groups were present — patients receiving ACT were younger, had less-aggressive primary tumour pathology, were less likely to receive adjuvant radiotherapy, and had less bilateral inguinal disease — all consistent with confounding by indication [11]. The authors themselves noted that prospective studies would be required to establish causality.

Complementary retrospective evidence from Necchi et al. (2017; n=201 across multiple European and Asian centres) confirmed that perioperative chemotherapy, whether administered in the neoadjuvant or adjuvant setting, was associated with improved recurrence-free survival compared with surgery alone, though the neoadjuvant approach appeared to confer a more favourable recurrence-free survival in comparative analyses [12]. A systematic review and meta-analysis by Paz Rojas et al. (2022; n=771) found no statistically significant OS advantage for ACT overall (HR 0.95; 95% CI 0.48–1.80), reflecting the substantial heterogeneity of the available retrospective evidence base and underscoring the absence of definitive proof of causal benefit [13].

ACT should therefore be viewed as a reasonable option for selected high-risk pN3 patients rather than a universally validated postoperative standard. The 2023 EAU–ASCO Guidelines recommend discussing ACT specifically with pN3 patients — a weak recommendation based on level-4 evidence [4]. Preferred regimens are cisplatin/taxane-based combinations; carboplatin/paclitaxel for cisplatin-ineligible patients; optimal timing 6–8 weeks after ILND.

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Adjuvant radiotherapy: Strongest rationale in locoregional risk control

ART draws its rationale from the established benefit of postoperative irradiation in other squamous cell carcinomas, particularly head and neck SCC. The most informative perioperative evidence in PSCC comes from Ager et al. (BJU International, 2021), a retrospective audit of 146 patients with pN3 PSCC treated with ART at two UK specialist centres between 2002 and 2017 [15]. All patients had undergone radical ILND; ENE was present in 99% of the cohort. Among the 125 patients who commenced ART, five-year RFS, CSS, and OS were 51%, 51%, and 44%, respectively [15]. A dose-response relationship was observed: doses ≤50 Gy were associated with a twofold higher rate of in-field recurrence compared with doses >50 Gy (31% vs. 14.2%). Although this difference did not reach statistical significance (p=0.13), the numerical trend has informed the adoption of 54 Gy in 27 fractions as the institutional standard at both centres and as the dose specified in the InPACT protocol [5,15]. These data suggest that dose intensity may matter in patients with ENE, though prospective confirmation is required. Notably, none of the patients in this cohort received adjuvant chemotherapy, and the authors noted that chemosensitisation might improve outcomes further [15].

Additional retrospective evidence supports the role of ART in selected populations. Tang et al. (2017; n=92) reported improved OS and DSS with adjuvant pelvic RT in pelvic node-positive patients [16], and Li et al. (2021; n=93) demonstrated that the addition of RT to chemotherapy improved survival specifically in patients with ENE, while chemotherapy alone appeared sufficient in those without extranodal spread [19]. Population-level NCDB data (Winters et al., 2018) suggested an OS benefit with ART even in pN1–N2 disease [17], though the retrospective nature of all these series limits causal interpretation. Using inverse probability weighting to adjust for confounding, Jaipuria et al. (2020; prospectively maintained registry, n=45) estimated that if all patients without pelvic nodal involvement received ART, average OS would be 1,438 days versus 1,007 days with chemotherapy alone (p<0.0001); notably, in patients with pelvic nodal involvement, CCRT offered no significant OS advantage over chemotherapy alone (estimated difference 17 days; p=0.21) [14]. HPV/p16 status may further modulate the response to irradiation, with emerging evidence of greater locoregional benefit in p16-positive tumours [18].

ART should therefore be interpreted as a selectively valuable modality, with its benefit probably greatest in patients with p16, ENE, multiple inguinal metastases, and absence of pelvic nodal disease, when adequate dose intensity can be delivered. The international InPACT contouring atlas (Cooper et al., IJROBP, 2025) now provides the first consensus on target volumes, dose-fractionation, and prepubic fat coverage for perioperative RT in PSCC [5].

Emerging immunotherapy combinations: Promising signal, predominantly from advanced disease

Recent phase II studies have introduced immune checkpoint inhibitors into the PSCC treatment landscape. The only perioperative ICI evidence currently available comes from An et al. (Cancer Cell, 2025), reporting the prospective phase II TNT trial (NCT04475016) in 29 patients with locally advanced PSCC [20]. The regimen — toripalimab (anti-PD-1) + nimotuzumab (anti-EGFR) + nab-TIP × 4 cycles, followed by consolidative surgery — achieved a pCR of 48.3% (95% CI: 29.4–67.5%) and ORR of 82.8% (95% CI: 64.2–94.2%), both the highest ever reported in PSCC in the perioperative setting. At a median follow-up of 39.97 months, two-year OS and PFS were 72.4% and 65.5%, respectively [20]. Biomarker analysis identified PD-L1 expression, TP53 wild-type status, and CD8+ T cell density as candidate predictive markers [20]. Grade 3–4 treatment-related adverse events occurred in 41.4% of patients, predominantly haematological; no treatment-related deaths were recorded. These results should be interpreted as the most promising contemporary perioperative signal rather than an established new standard, given the single-centre design, small sample, and absence of a control arm.

Although conducted in advanced or metastatic disease rather than the perioperative setting, three phase II trials provide important biological context. They are included not as evidence of perioperative efficacy, but to illustrate the activity spectrum and biomarker landscape of checkpoint inhibition across the PSCC disease course.

HERCULES (Cotait Maluf et al., JAMA Oncology, November 2025; n=33 evaluable) evaluated pembrolizumab + cisplatin/5-FU in first-line advanced PSCC not amenable to curative intent,

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demonstrating ORR 39.4%, mPFS 5.4 months, and mOS 9.6 months [21]. Exploratory biomarker analysis identified HPV-positive patients (ORR 55.6%) and TMB-high patients (ORR 75%) as enriched responders, while PD-L1 expression showed no clear predictive association despite being positive in 78.4% of patients [21]. EPIC-A (Bahl et al., ASCO GU 2025; n=29) evaluated cemiplimab + cisplatin-based chemotherapy, achieving CBR 62.1% at 12 weeks (48.3% at 21 weeks), mPFS 6.2 months, and mOS 15.5 months [22] — results consistent with HERCULES and collectively reinforcing the activity of ICI combined with chemotherapy in PSCC. In contrast, ALPACA (Sridhar et al., ESMO 2025 LBA37; n=23 evaluable) evaluated avelumab monotherapy in platinum-refractory advanced PSCC and achieved ORR 17%, with durable responses in responders (median duration 15.9 months), but mPFS of only 1.7 months and mOS of 3.9 months [23]. The trial required over seven years to recruit 25 patients across three Canadian centres.

Taken together, these trials converge on a consistent message: ICI monotherapy provides limited and unpredictable benefit in unselected advanced PSCC, whereas ICI combined with chemotherapy yields meaningfully higher response rates. This pattern directly informs the rationale for incorporating ICI into perioperative combination regimens in earlier-stage, lower-burden disease. These findings support the biological rationale for perioperative investigation, but do not establish perioperative efficacy.

The sequencing question: NAC versus adjuvant therapy

The fundamental unresolved clinical question — whether to deliver systemic therapy before or after surgery — has no randomised answer. The case for NAC rests on in-vivo chemosensitivity assessment, potential for curative downstaging, and early identification of non-responders before committing to morbid surgery [6,9]. The Rose et al. data demonstrate this starkly: clinical responders achieve median OS of 73 months versus 17 months in non-responders [9]. The primary clinical concern with NAC is disease progression during chemotherapy in the 30–50% who do not respond, with possible loss of the surgical window — a risk particularly relevant in cN1 patients where early ILND alone may be curative.

The case for the adjuvant approach rests on complete pathological staging before systemic exposure and the therapeutic benefit of upfront radical surgery [12]. Population-level data suggest that NAC confers superior OS over ACT in cN2–N3 disease [4], though the meta-analysis by Paz Rojas et al. found no statistically significant difference in OS between the two approaches overall, reflecting the heterogeneity of available evidence [13].

The 2023 EAU–ASCO Guidelines operationalise this tension pragmatically: NAC for cN2–N3 chemotherapy-fit patients; surgery first with discussion of adjuvant therapy for cN1 [4]. InPACT (NCT02305654) addresses this directly through a three-arm first randomisation — upfront ILND versus NAC-TIP followed by ILND versus neoadjuvant CCRT followed by ILND — and a secondary pelvis randomisation comparing adjuvant CCRT versus prophylactic PLND in high-risk post-ILND patients [5,24]. Recruitment was completed or near completion as of mid-2025, with results anticipated in 2027–2028.

Biomarkers and quality of life

The transition toward biomarker-driven perioperative therapy represents the defining challenge of the next decade. HPV/p16 status — now recommended for routine reporting [4] — is the most clinically actionable classifier, with emerging evidence of differential benefit from both systemic therapy and irradiation [18,20,21]. TP53 mutation status identifies the high-risk HPV-independent population with potential resistance to both chemotherapy and immunotherapy [2]. TMB-high status, present in only 10–15% of PSCC tumours, consistently associates with higher ORR to ICI+chemotherapy combinations [21], while PD-L1 expression alone has not reliably predicted response [21]. Combinatorial biomarker panels will likely be required for effective patient selection in future perioperative ICI trials.

Quality of life remains a non-negotiable treatment dimension. Centralisation in expert multidisciplinary centres — recommended by EAU–ASCO 2023 and ESMO-EURACAN 2024 [4] — remains essential to ensure systematic biomarker assessment, access to trials, and integration of organ-preservation and psychosexual rehabilitation strategies.

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Limitations

Several important limitations of the available evidence must be acknowledged. Penile cancer is an exceptionally rare malignancy, which has precluded the conduct of adequately powered randomised trials; to date, no phase III trial in the perioperative setting has published efficacy results [24]. The evidence base for this review consists predominantly of retrospective single-institution and multicentre cohorts, population-based registry analyses, and small single-arm phase II trials, all carrying substantial risk of confounding by indication, selection bias, and institutional variability in surgical technique, chemotherapy regimens, and radiotherapy dose and volumes [11–19]. Patient populations are heterogeneous across studies, with differences in nodal burden (pN1–pN3), HPV status, prior treatment, and extent of lymphadenectomy limiting cross-study comparisons. Outcome endpoints are not uniformly defined, and follow-up durations vary considerably.

The inclusion of data from trials conducted in advanced or metastatic PSCC — HERCULES, EPIC-A, and ALPACA — to contextualise perioperative ICI development represents extrapolation from a biologically and clinically distinct population [21–23]. Such extrapolation is hypothesis-generating at best and should not be interpreted as evidence of perioperative benefit. Overlap between patient cohorts across retrospective series from the same institutions cannot be excluded. The dose-response relationship for ART observed by Ager et al. did not reach statistical significance (p=0.13) [15], and the inverse probability weighting-adjusted survival estimates reported by Jaipuria et al. should be interpreted as modelled averages under specific assumptions rather than directly observed outcomes [14]. Finally, this review did not apply a formal risk-of-bias assessment tool, and the conclusions reflect narrative synthesis of a body of evidence that is inherently weak and awaiting validation through ongoing randomised trials, primarily InPACT [5,24].

CONCLUSIONS

Current evidence supports cisplatin/taxane-based NAC as the most established perioperative strategy for selected cN2–N3 PSCC, with clinical responders achieving substantially longer survival than non-responders (median OS 73 vs. 17 months) [9]. ACT and ART may be associated with improved outcomes in selected pN2–N3 patients after lymphadenectomy, particularly in the presence of ENE, but the available evidence is predominantly retrospective and vulnerable to confounding [11–17,19]. For ART, available retrospective data suggest that lower dose intensity may compromise in-field control in patients with ENE, and the 54 Gy standard adopted in the InPACT protocol provides a reasonable contemporary reference pending prospective validation [5,15]. The TNT regimen represents the most encouraging perioperative immunotherapy signal to date (pCR 48.3%, ORR 82.8%) [20], while phase II data confirm that ICI combined with chemotherapy is active in advanced PSCC [21,22]; ICI monotherapy, however, demonstrates insufficient activity in unselected patients [23]. Until InPACT (NCT02305654) provides the first randomised evidence [5,24], treatment decisions should remain individualised within experienced multidisciplinary centres, incorporating clinical stage, nodal burden, pathological risk factors, and HPV/p16 biomarker status.

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