APPENDIX

Table 1. Key studies on perioperative systemic therapy and radiotherapy in node-positive penile squamous cell carcinoma

Study (Year)	Clinical setting	Design/phase	n	Intervention	ORR	Key survival outcome	LoE	Main limitation	Key message
Pagliaro 2010 [5]	Perioperative (NAC)	Phase II prospective	30	TIP (paclitaxel + ifosfamide + cisplatin)	50%	Median OS 17.1 mo; pCR 10%	2b	Prospective, single-arm, small n, slow accrual over 8 yrs	Historical reference NAC regimen; DFS 67% in surgical responders
Nicholson 2013 [6]	Perioperative (NAC)	Phase II prospective	29	TPF (docetaxel + cisplatin + 5-FU)	38.5%	Median OS 14 mo	2b	Phase II, primary endpoint not met, significant haematotoxicity	TPF did not meet primary endpoint; toxicity limits routine use; TIP preferred
Djajadiningrat 2015 [7]	Perioperative (NAC)	Phase II prospective	26	TPF (docetaxel + cisplatin + 5-FU)	44%	Median OS 10 mo; pCR 4%	2b	Phase II, single-arm, small n	Low pCR (4%) supports preference for TIP-based NAC over TPF
Azizi 2020 [9]	Perioperative (NAC)	Systematic review & meta-analysis	182	NAC platinum-based (10 studies)	53%	Pooled: pCR 16%	2a	Meta-analysis of heterogeneous retrospective and prospective series	Best pooled evidence for NAC; taxane-platinum regimens yield highest ORR
Necchi 2017 [11]	Perioperative (NAC/ACT)	Retrospective multicentre	201	Perioperative QT (NAC or ACT; multiple regimens)	—	NAC associated with superior RFS vs. ACT ($p<0.05$)	3	Retrospective, heterogeneous timing and regimens, no control arm	Retrospective signal favouring NAC over ACT for RFS; hypothesis-generating only.
Rose 2024 [8]	Perioperative (NAC)	Retrospective multicentre (11 centres, 4 continents)	209	NAC platinum-based (73% TIP)	57.2%	Median OS 73 vs. 17 mo† (responders vs. non-responders)	3	Retrospective, responder-selection bias, no randomised comparator	Clinical response strongly associated with survival outcome.
Sharma 2015 [10]	Adjuvant (ACT)	Retrospective multicentre (4 centres)	84	ACT cisplatin-based (pN3 only)	—	Median OS 21.7 vs. 10.1 mo† (HR 0.40; p=0.021)	3	Retrospective, confounding by indication, imbalanced baseline characteristics	ACT independently associated with improved OS in pN3; causality not established

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Jaipuria 2020 [13]	Adjuvant (ART)	Prospectively maintained single-centre registry; IPTW analysis	45	ART vs. QT (groin-only disease); CCRT vs. QT (pelvic disease)	—	Estimated avg OS: ART 1,438 vs. QT 1,007 days†† ($p<0.0001$); no advantage with pelvic disease	3	Non-randomised, small n, IPTW-modelled estimates, single centre	ART associated with longer OS than QT in patients without pelvic involvement; CCRT not superior in pelvic disease
Tang 2017 [15]	Adjuvant (ART)	Retrospective multicentre (4 centres)	92	Adjuvant pelvic RT vs. no RT (pN3, pelvic node-positive)	—	Median OS 12.2 vs. 8.0 mo† ($p=0.04$); DSS 14.4 vs. 8.0 mo ($p=0.02$)	3	Retrospective, short median follow-up (9.3 mo), heterogeneous RT doses	Adjuvant pelvic RT associated with improved OS and reduced recurrence in pelvic node-positive PSCC
Li 2021 [18]	Adjuvant (ART + ACT)	Retrospective multicentre	93	RT + QT vs. QT alone (pN3 + ENE)	—	Superior OS and CSS with RT+QT vs. QT alone	3	Retrospective, confounding by indication, heterogeneous chemotherapy regimens	Addition of RT to QT improves survival specifically in ENE-positive pN3; supports combined modality approach
Ager 2021 [14]	Adjuvant (ART)	Retrospective multicentre (2 UK centres)	146	ART for pN3 (54 Gy/27 fr standard since 2016)	—	5-yr RFS 51%; CSS 51%; OS 44%	3	Retrospective, no control arm, heterogeneous doses pre-2016, no adjuvant QT	Lower dose was associated with numerically higher in-field recurrence; contemporary practice has shifted toward ≥54 Gy in ENE
An 2025 [19]	Perioperative (NAC + ICI)	Phase II prospective, single-arm	29	TNT: toripalimab + nimotuzumab + nab-TIP × 4 cycles → surgery	82.8%	pCR 48.3%; 2-yr OS 72.4%; 2-yr PFS 65.5%	2b	Phase II, single-arm, small n, single Asian centre, no control arm	Highest pCR and ORR ever reported in PSCC; most promising perioperative ICI signal; requires broader validation
HERCULES 2025 [20]	Advanced/metastatic (1st line)	Phase II, single-arm (11 Brazilian centres)	33 eval.	Pembrolizumab + cisplatin/carboplatin + 5-FU → pembro maintenance	39.4%	Median OS 9.6 mo; mPFS 5.4 mo; HPV+ ORR 55.6%; TMB-high ORR 75%	2b	Phase II, single-arm, all Brazilian centres, indirect perioperative evidence	Validates ICI+QT activity in PSCC; biomarker enrichment (HPV+, TMB-high) essential for future trial design

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EPIC-A 2025 [21]	Advanced/metastatic (1st line)	Phase II, open-label, non-randomised, multicentre (UK)	29	Cemiplimab + cisplatin-based QT × 4 cycles → cemiplimab maintenance (2 yrs)	51.7%	CBR 62.1% at 12 wks (48.3% at 21 wks); mPFS 6.2 mo; mOS 15.5 mo	2b	Phase II, single-arm, indirect perioperative evidence, short follow-up	Consistent with HERCULES; supports ICI+QT as active combination in advanced PSCC warranting perioperative evaluation
ALPACA 2025 [22]	Advanced/metastatic (2nd line)	Phase II, investigator-initiated, single-arm, multicentre (Canada)	23 eval.	Avelumab monotherapy 10 mg/kg IV q2w	17%	mDOR 15.9 mo in responders; mPFS 1.7 mo; mOS 3.9 mo	2b	Highly pretreated population (96% prior platinum, 83% visceral mets), indirect perioperative evidence	ICI monotherapy shows limited activity in unselected late-line PSCC; supports prioritisation of combination strategies in earlier disease settings

Colour coding: Blue = Perioperative NAC; Green = Adjuvant chemotherapy; Orange = Adjuvant radiotherapy; Purple = Perioperative ICI; Red = Advanced/metastatic context only.

† Responders vs. non-responders or intervention vs. control arm. †† Inverse probability treatment weighting-modelled average OS estimates; not directly observed Kaplan-Meier medians. ACT = adjuvant chemotherapy; ART = adjuvant radiotherapy; CBR = clinical benefit rate; CCRT = concurrent chemoradiotherapy; DFS = disease-free survival; DSS = disease-specific survival; ENE = extranodal extension; ICI = immune checkpoint inhibitor; IPTW = inverse probability treatment weighting; LoE = level of evidence (Oxford CEBM 2011); mDOR = median duration of response; mPFS = median progression-free survival; NAC = neoadjuvant chemotherapy; OS = overall survival; pCR = pathological complete response; QT = chemotherapy; RFS = recurrence-free survival; TIP = paclitaxel + ifosfamide + cisplatin; TNT = toripalimab + nimotuzumab + nab-TIP; TPF = docetaxel + cisplatin + 5-fluorouracil. No phase III randomised controlled trial data are currently available in the perioperative setting; InPACT (NCT02305654) is ongoing.