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European Association of Urology

Review – Penile Cancer

Management of Lymph Node–positive Penile Cancer: A Systematic Review

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Abstract

Context: Lymph node (LN) involvement in penile cancer is associated with poor survival. Early diagnosis and management significantly impact survival, with multimodal treatment approaches often considered in advanced disease.
Objective: To assess the clinical effectiveness of treatment options available for the management of inguinal and pelvic lymphadenopathy in men with penile cancer.

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Evidence acquisition: EMBASE, MEDLINE, the Cochrane Database of Systematic Reviews, and other databases were searched from 1990 to July 2022. Randomised controlled trials (RCTs), nonrandomised comparative studies (NRCSs), and case series (CSs) were included.
Evidence synthesis: We identified 107 studies, involving 9582 patients from two RCTs, 28 NRCSs, and 77 CSs. The quality of evidence is considered poor. Surgery is the mainstay of LN disease management, with early inguinal LN dissection (ILND) associated with better outcomes. Videoendoscopic ILND may offer comparable survival outcomes to open ILND with lower wound-related morbidity. Ipsilateral pelvic LN dissection (PLND) in N2–3 cases improves overall survival in comparison to no pelvic surgery. Neoadjuvant chemotherapy in N2–3 disease showed a pathological complete response rate of 13% and an objective response rate of 51%. Adjuvant radiotherapy may benefit pN2–3 but not pN1 disease. Adjuvant chemoradiotherapy may provide a small survival benefit in N3 disease. Adjuvant radiotherapy and chemotherapy improve outcomes after PLND for pelvic LN metastases.
Conclusions: Early LND improves survival in nodal disease in penile cancer. Multimodal treatments may provide additional benefit in pN2–3 cases; however, data are limited. Therefore, individualised management of patients with nodal disease should be discussed in a multidisciplinary team setting.
Patient summary: Spread of penile cancer to the lymph nodes is best managed with surgery, which improves survival and has curative potential. Supplementary treatment, including the use of chemotherapy and/or radiotherapy, may further improve survival in advanced disease. Patients with penile cancer with lymph node involvement should be treated by a multidisciplinary team.

1. Introduction

Penile cancer (PeCa) is a rare malignancy with an incidence of 1 in 100 000 males but has favourable survival when organ-confined. Approximately one-third of cases will have metastasis to inguinopelvic lymph nodes (LNs), which is prognostic for mortality. Up to 25% of those with impalpable LNs will harbour micrometastasis, while the rate of metastasis is higher among cases with palpable LNs. Therefore, the European Association of Urology (EAU) recommends treatment of both the primary lesion and LNs to improve survival [1].

According to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM criteria, pathological nodal staging is defined as follows: pN1 = up to two unilateral inguinal LN (ILN) metastases without extranodal extension (ENE); pN2 = $\geq$3 unilateral or bilateral ILN metastases without ENE; and pN3 = ENE of ILN metastases or pelvic LN metastases.

Radical LN surgery remains the cornerstone of management for early nodal disease (cN1–2) but is associated with significant morbidity and the benefit of adjuvant treatments is uncertain. Nodal surgery alone is often not curative in cases of extensive LN involvement [1,2]. Therefore, multimodal treatment approaches with (neo)adjuvant chemotherapy and/or radiotherapy (RT) are often considered.

We systematically reviewed evidence on the clinical effectiveness of various approaches for management of LN-positive PeCa as part of the process for developing the 2023 EAU-American Society of Clinical Oncology guideline.

2. Evidence acquisition

2.1. Search strategy

The review protocol was registered on PROSPERO (CRD42021290784). EMBASE, MEDLINE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL; Cochrane HTA, DARE, HEED), and ClinicalTrials.gov were searched from 1990 to June 30, 2022. Reference lists from the publications identified were also searched. Only English language articles were included. The search strategy is provided in the Supplementary material. Eight reviewers (Fig. 1) screened abstracts and full-text articles in pairs. Conflicts were independently reviewed and arbitrated by a senior author (V.I.S.). Reviewers performed data extraction, which was verified by a senior author (V.I.S.).

2.2. Types of study design included

Peer-reviewed retrospective and prospective studies addressing co-primary or secondary outcomes after LN management were eligible (minimum n = 15). Conference abstracts, case reports, and narrative reviews were excluded. Studies on secondary penile carcinoma, non–squamous cell carcinoma, and primary urethral carcinoma were excluded unless they included data on patients with primary penile squamous-cell carcinoma and results were separately reported.

2.3. Types of participant included

Patients with PeCa of any stage, diagnosed with clinically apparent (cN+) or pathologically confirmed (pN+) inguinal and/or pelvic LN disease who received treatment with any intent were included.

2.4. Types of intervention included

All treatments for nodal disease management, including surgery, RT, chemotherapy, targeted therapy, or combinations of treatments with any pairwise comparisons were allowed.

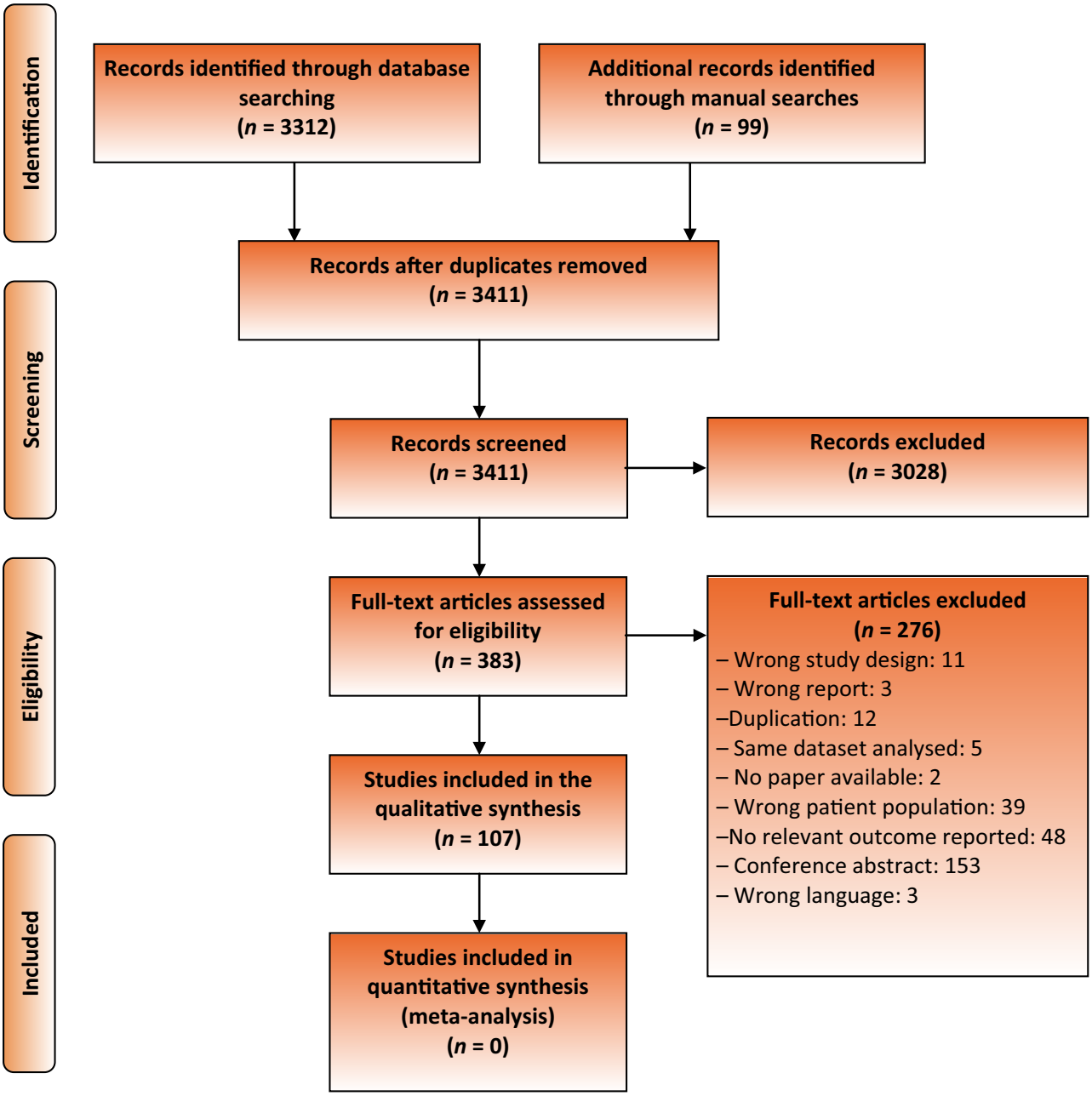

Fig. 1 – Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2009 flow diagram of the study selection process.

2.5. *Outcome measures*

The primary outcome was 5-yr overall survival (OS). Co-primary endpoints included 5-yr cancer-specific survival (CSS), 5-yr recurrence-free survival (RFS), and patient reported outcomes measured with validated questionnaires. Secondary outcomes were 1- and 2-yr OS and CSS, 1- and 2-yr regional and distant recurrence, progression to advanced disease stage, and treatment-related complications.

2.6. *Assessment of risk of bias*

Randomised controlled trials (RCTs) were assessed for risk of bias (RoB) using the Cochrane RoB assessment tool [3]. RoB for non-randomised controlled studies (NRCSs), including items to assess risk of confounding bias, was assessed using the ROBINS-I tool [3]. Five confounders were identified *a priori*: tumour stage, tumour grade, coexisting metastatic disease, older age, and previous RT or chemotherapy. For case series (CSs), a five-criterion quality appraisal checklist was used [4].

2.7. *Data analysis*

Only two RCTs were included; therefore, a quantitative analysis was not appropriate. Planned subgroup analysis for disease stage for outcomes at specific time points was not possible because of low evidence quality; therefore, a qualitative synthesis of outcomes was performed.

3. Evidence synthesis

3.1. Quantity of evidence identified

Overall, 3411 abstracts were screened and 383 studies were retrieved for full-text screening. A total of 107 studies involving 9582 patients were eligible for inclusion [5–112]: two RCTs (91 patients), 28 NRCSs (3047 patients), and 77 CSs (6444 patients). The study selection process is shown in Figure 1.

3.2. Study characteristics

3.2.1. RCT characteristics

Two RCTs were identified [5,6]: one compared laparoscopic versus open ILND [6] and the other assessed the use of vacuum-assisted wound closure versus conventional wound care [5].

3.2.2. NRCS characteristics

Three NRCSs assessed adjuvant RT (ART) [7–9], three compared adjuvant chemoradiotherapy (ACRT) to RT [10–12], three compared neoadjuvant with adjuvant chemotherapy (ACT) [13–15], two compared systemic therapy to no therapy [16,17], 15 compared different ILND techniques [32,60,68,78,81,89,95,97,99–104,107], and two compared outcomes after pelvic LN dissection (PLND) [18,19].

3.2.3. CS characteristics

Ten studies assessed ART [20–29], three assessed ACRT [30,31,111], eight assessed neoadjuvant chemotherapy (NACT) [33–40], 11 assessed adjuvant systemic therapy outcomes [41–51], 39 assessed ILND outcomes [69–107], and six evaluated PLND outcomes [52–57]. Six were prospective studies [36–38,45,49,58] and the remainder were retrospective analyses.

3.3. RoB and confounding assessment for the studies included

The RoB assessments for RCTs and NRCSs are summarised in Figure 2. All NRCSs were assessed as having high RoB. Selection, performance, detection, and attrition biases were high for the majority of the studies, while reporting bias was unclear or high. All CSs had high RoB.

3.4. Qualitative synthesis of the results

3.4.1. Management of inguinal LN disease

3.4.1.1. Surveillance. Two NRCSs compared surveillance to ILND and RT in patients with clinically suspected nodes [59,60]. Despite limited numbers, both studies reported higher regional recurrence rates (63% and 60%) in comparison to ILND or RT.

3.4.1.2. ILND. Radical ILND remains the standard of care for positive resectable nodes. Outcomes for 5863 men who underwent ILND are reported [23,24,26,32,59,63,66,67,69–107]. Survival data were available for 2069 patients, with 5-yr OS of 40–74% and 5-yr CSS of 41–55% (Supplementary Table 1). The cumulative mean 5-yr OS and CSS rates were 43% and 45% [69–75], respectively. The cumulative mean 1-yr OS and CSS rates were 71% and 70%, respectively.

In low-volume disease (ie, pN1), ILND is curative in most patients, with small cohorts showing equivalence with pN0 disease [59,79,80]. It is worth noting that in 2017 the AJCC updated the TNM staging, changing the pN1 definition from one node to up to two unilateral nodes, and thus contemporary series may report lower survival. With more than two positive inguinal nodes and the presence of extranodal extension (ENE), the risk of pelvic node involvement is 23% and 56%, respectively [52,53]. Bilateral inguinal nodal involvement reduces 5-yr OS (86% vs 60%), RFS (76% vs 60%), and CSS (68% vs 51%) [26,61,74], although a significant reduction was seen in only one study and three others reported no significant reduction in comparison to patients with unilateral LN involvement [24,58,61,75].

The presence of ENE is strongly prognostic: 5-yr OS is 30–60%, which is significantly lower than for ENE-negative disease (75–85%) [26,59,61,75]. On multivariable analysis, most studies showed that ENE was associated with significantly worse survival [24,61,75].

After ILND, recurrence occurs in approximately 30% of cases, mostly as inguinal, pelvic, or distant recurrence within 48 mo. The main predictors of recurrence are pT3/4 (hazard ratio [HR] 1.6), pN2 (HR 2.4), and pN3 (HR 6.4), with 5-yr OS of <16% [76].

3.4.1.2.1. Factors predicting ILND efficacy. Approximately 20–25% patients staged as cN0 at physical examination/imaging still harbour (micro)metastasis. Therefore, surveillance and delayed ILND in cN0 disease may risk missing a curative opportunity (Supplementary Table 2) [77]. Early lymphadenectomy (LND) improves 3- and 5-yr RFS (Supplementary Table 3) in node-positive patients. Delaying ILND beyond 3 mo is detrimental, particularly in high-risk disease (grade 3 or ≥T1b stage) [67,78] or cases with nodal metastasis on dynamic sentinel node biopsy [59,79–81].

Higher nodal yield at LND (≥8 LNs [66,82,83] to 15–16 LNs [83–85]) may be associated with better 5-yr survival (Supplementary Table 4). Analysis of the US Surveillance, Epidemiology and End Results (SEER) database showed that removal of more than five negative LNs led to better survival [86]. These results require cautious interpretation, as nodal yield may be a confounder for extent of dissection rather than a true independent prognostic marker. Similarly, LN density, the proportion of positive versus negative LNs, with density cutoffs ranging from 6.7% to 22%, was associated with better survival and may be a better predictor than pN staging (Supplementary Table 5) [58,69,83,85,87]. However, the survival benefit observed may be due to stage migration.

3.4.1.2.2. Complications after ILND. ILND is associated with significant morbidity (Supplementary Table 6). Wound complications (infection, necrosis, dehiscence), lymphoedema, and lymphocele occur in up to 50% of cases [63,73,88–91]. Modified ILND is associated with fewer complications [88,89,92], although others have reported similar rates to those with radical ILND [93]. A higher risk of complications is seen with sarcopenia (odds ratio [OR] 4.8) and elevated body mass index (OR 1.76 for each 5.8-kg/m^2 increase) [91,94].

Various technical modifications may influence ILND morbidity. Sartorius muscle transposition doubles the risk

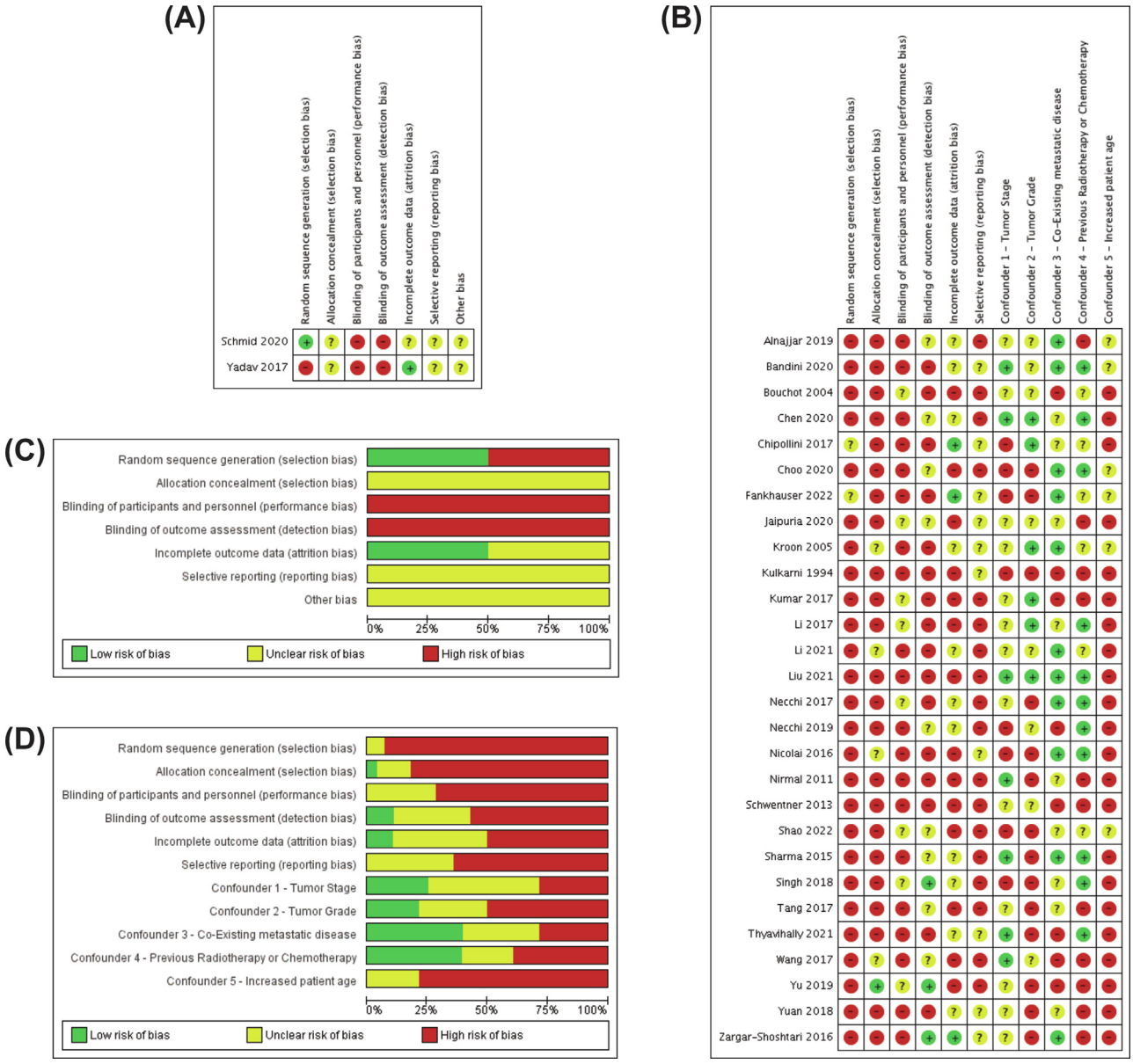

Fig. 2 – Risk-of-bias (RoB) assessment for (A) randomised controlled trials and (B) nonrandomised comparative studies. Summary of the RoB assessment for (C) randomised controlled trials and (D) nonrandomised comparative studies.

of grade ≥2 complications [91]. Preservation of the fascia lata while excising deep nodes is feasible, with lower complication rates in comparison to radical ILND (mostly in cN0–N2 cases) [92]. Myocutaneous flap reconstruction (MFR) with a tensor fasica lata (TFL) or a vertical rectus abdominus myocutaneous flap to aid wound closure has been reported [95–97]. Whilst MFR is feasible and may have a role in cN3 disease, complications appeared to be higher than with standard closure, although some studies reported significantly lower wound necrosis [93]. Routine use of a wound vacuum device or a TFL flap did not significantly impact drain fluid output, drain indwelling time, or wound complication rates [5,97]. Different skin incisions either result in no difference in complications or higher skin-edge necrosis rates with S- and T-shaped incisions [98,99].

3.4.1.2.3. Minimally invasive ILND. Given the morbidity of open ILND, minimally invasive techniques have been explored (Table 1). (Robot-assisted) videoendoscopic inguinal lymphadenectomy (VEIL or RAVEIL) was feasible in small series with ports in the femoral triangle apex or in the hypogastrium [32,100]. Although the operative time is longer, LN yields can be similar to those with open ILND, with lower lymphoedema rates [100–102]. Length of stay and drain indwelling time were shorter with VEIL or RAVEIL and wound complication rates were lower, though lymphocele and readmission rates were equivalent [68,99–107]. The saphenous vein was spared more frequently in minimally invasive ILND than in open ILND [32,101,105].

Robust comparisons of oncological outcomes are limited by short follow-up (6–50 mo) among minimally invasive

Table 1 – Studies comparing open inguinal lymph node dissection with MITs

Study	Year	MIT	Patients (*n*)	OT (min)	LoS (d)	Drain dwell time (d)	Complications	VEIL FU (mo)	pN0 in VEIL (%)
Schwentner [103]	2013	VEIL	42	VEIL: 136* OILND: 102	NR	NR	Overall: VEIL 7.1%, OILND 56%*	55	71
Wang [104]	2017	VEIL	34	VEIL: 140 OILND: 170	VEIL: 10.4 OILND: 12.5	VEIL: 7.2 OILND: 11.4*	Skin necrosis: VEIL 5.3%, OILND 29%* Wound infection: VEIL 5.3%, OILND 14% Lymphoedema: VEIL 16%, OILND 29% Lymphocele: VEIL 0%, OILND 24%*	NR	38
Kumar [100]	2017	VEIL	42	VEIL: 97 OILND: 94	VEIL: 2.3 OILND: 7.3*	NR	Wound-related: VEIL 6%, OILND 68%* Lymphoedema: VEIL 3%, OILND 37%* Lymphocele: VEIL 27%, OILND 20%	16	NR
Russell [105]	2017	VEIL RAVEIL	34	RAVEIL: 137 VEIL: 141	RAVEIL: 1 VEIL: 1	RAVEIL: 36 VEIL: 42	Skin-related: VEIL 14%, RAVEIL 7% Lymphatic: VEIL 14%, RAVEIL 4%	5.5	67
Singh [102]	2018	RAVEIL	151	RAVEIL: 75 OILND: 60*	RAVEIL: 3 OILND: 4*	RAVEIL: 12 OILND: 15*	Skin necrosis: RAVEIL 9.8%, OILND 23%* Severe lymphoedema: RAVEIL 0%, OILND 9%* Lymphocele + SSI: ND	41	61
Yu [107]	2019	RAVEIL	19	RAVEIL: 69 OILND: NR	NR	NR	Skin-related: RAVEIL 0%, OILND 45% Lymphorrhoea: RAVEIL 55%, OILND 40% Lymphocele: RAVEIL 11%, OILND 0%	25	22
Thyavihally [68]	2021	VEIL or RAVEIL	79	VEIL: 90* OILND: 110	VEIL: 6.1 OILND: 9.6*	NR	Wound infection: VEIL 8%, OILND 42%* Skin necrosis: VEIL 0%, OILND 24%* Lymphocele: VEIL 20%, OILND 24% Lymphoedema: VEIL 11%, OILND 14%	42	28
Fankhauser [101]	2022	VEIL	206	VEIL: 185* OILND: 120	VEIL: 2 OILND: 4*	VEIL: 13 OILND: 13	Wound infection: VEIL 38%, OILND 27% Skin necrosis: VEIL 0%, OILND 6%* Lymphocele: VEIL 18%, OILND 7%* Lymphoedema: VEIL 20%, OILND 14%*	21	NR
Shao [99]	2022	VEIL	109	VEIL: 60 OILND: 64	VEIL: 9 OILND: 14*	VEIL: 11 OILND: 8*	Wound complications: VEIL 11%, OILND 30%* Flap necrosis: VEIL 1.3%, OILND 2.2% Lymphocele: VEIL 14%, OILND 13% Lymphoedema: VEIL 27%, OILND 30%	43	65

MIT = minimally invasive technique; OT = operating time; LoS = length of stay; VEIL = videoendoscopic inguinal lymphadenectomy; RAVEIL = robot-assisted VEIL; OILND = open inguinal lymph node dissection; FU = follow-up; SSI = surgical site infection; NR = not reported; ND = none detected.
* Statistically significant difference.

studies. Three studies compared cancer outcomes between open and endoscopic approaches with median follow up of >40 mo [68,103]. There were similar local recurrence rates [103], and no difference in 5-yr OS and disease-specific survival (DSS) between the two approaches [68,99]. Minimally invasive ILND was used mainly in cN0 disease, with most series having high pN0 rates, which may reflect a selection bias. Only two series used VEIL in proven LN disease [100,101]. Therefore, it is too early to draw conclusions about the oncological safety of VEIL in node-positive disease. Moreover, some studies that used open ILND as a comparator occasionally included steps associated with a higher risk of complications such as sartorius transposition and saphenous vein sacrifice that were not performed in minimally invasive procedures.

3.4.1.3. Neoadjuvant treatment.

3.4.1.3.1. Neoadjuvant chemotherapy. NACT is usually reserved for fixed/bulky inguinal or pelvic LNs (ie, cN2–3) to reduce the tumour burden and improve the feasibility and outcomes of resection. However, while NACT is mostly used for cN2–3 disease, some studies included cN1 cases.

Table 2 – Neoadjuvant and primary nonsurgical treatments

Study by treatment type	Design	Patients (*n*)		Characteristics	Selection criteria for treatment	Treatment regime	Response rate	Survival outcome	Toxicity
		Total	N+ M0						
Primary or salvage systemic therapy									
Necchi 2018 [45]	Phase 2	28	20	Tx cN2–3 M0–1	cN2–3 and/or M1	Dacomitinib	ORR 32%	Median OS (M0): 20 mo 1-yr OS (M0): 64%	G3–4 CPs: 10%
Carthon 2014 [41]	RS	24	9	T2–4 N2–3 M0–1	T4 or N2–3 or M1	Cetuximab or erlotinib or fefitinib alone Cetuximab + Pt Cetuximab + TIP	ORR 33% (N + M0)	Median OS (N+ M0): 6.0 mo	G1/2 rash: 71% G3–4: 16% Mortality: 4%
Primary CT									
Nicholson 2013 [36]	Phase 2	29	21	T3–4 N1–3 M0–1	M1, or N2–3 M0 or T3 N1 M0 or T4 Nx M0	Docetaxel, CSP, + 5FU	ORR (M0) 37%	Median OS: 14 mo 1-yr OS: 63%	G3–4 CPs: 68%
NACT									
Pagliaro 2010 [37]	Phase 2	30	30	Tx N2–3 M0	N2–3 M0	Paclitaxel, ifosfamide, CSP	ORR 50%	Median OS: 17 mo	G3–4 CPs: 53%
Theodore 2008 [38]	Phase 2	28	8	T3–4 N1–3 M0–1	T3–4 or N1–3 or M1	Irinotecan + CSP	ORR NACT 29%	NR	G3–4 CPs: 66%
Bandini 2020 [112]	MCRS[a]	334	76	T1–4 cN1–3 undergoing ILND	NR	ICT (TPF or PF) vs no ICT	NR	2-yr OS: 58% vs 70% ($p > 0.05$) 2-yr survival benefit with ICT in eligible patients (23%)	NR
Necchi 2019 [15]	MCRS	689	86	T1–4 cN0–3 undergoing ILND	NR	ICT (Pt-based) vs no ICT	NR	5-yr OS: cN0: 65% vs 70% cN1–2: 45% vs 62% cN3: 45% vs 25%	NR
Necchi 2017 [13]	MCRS	201	94	T3–4 N0 or T1–4 N1–3	NR	ICT or ACT or ICT + ACT	ORR 53% pCR 17%	1-yr OS: ICT 61.3%, ICT + ACT 75% 2-yr OS: ICT 36%, ICT + ACT 32%	G3–4 CPs: ICT 58% ICT + ACT 100%
Dickstein 2016 [33]	RS	61	54	T1–4 N1–3 M0	cN1–3 with intent for ILND	TIP (88%)	ORR 65% pCR 16%	Median OS: 26 mo 2-yr OS: 43% 5-yr OS: 33%	NR
Nicolai 2016 [14]	RS	47	28	T1–4 N2–3 M0	cN3 or bilateral disease	ICT (TPF) or ACT (TPF)	ORR 43% pCR 14%	2-yr OS: 30%	≥G3 AEs: 85% Toxic death: 3.5%
Djajadiningrat 2015 [34]	NRRS	26	26	T4 N0 M0 or T1–4 N3 M0	T4 N0 M0 or T1–4 N3 M0	TPF	ORR 44% pCR 4%	Median OS: 10 mo 1-yr OS: 46% 2-yr OS: 27%	G3–4 CPs: 58%
Zou 2014 [40]	RS	24	24	T1–3 N3 M0	N3 penile SCC	BMP	ORR 63%	1-yr OS: 71% 2-yr OS: 50% 5-yr OS: 46%	G3–4 CPs: 5%
Leijte 2007 [35]	RS	20	20	T1–4 N0–3 M0	Inoperable local or regional penile SCC	Bleomycin or VBM or PF or BMP	ORR 63%	5-yr OS: 32%	Severe toxicity: 20% Toxic deaths: 15% (BMP or VBM)
Xu 2019 [39]	RS	19	19	Tx N3 M0	N3 penile SCC	TIP	ORR 63%	Median OS: 23 mo	G3–4 Myelosuppression: 16%; G3–4 nausea/vomiting: 5%
Neoadjuvant RT									
Ravi 1994 [28]	RS	285	45	T1–4 N+	ILNs ≥4 cm and mobile or cN3	40 Gy	ORR: ILNs ≥4 cm 18% cN3 14%	5-yr DFS: ILN ≥4 cm 70% cN3 17%	NR
Primary RT									
Kulkarni 1994 [60]	RS	64	18	T1–3 cN0–2A	T any N0–2A	50-Gy RT or ILND or surveillance	NR	5-yr OS in cN+: RT 50%	RT: Lymphoedema 16%

(*continued on next page*)

Table 2 (*continued*)

Study by treatment type	Design	Patients (*n*)		Characteristics	Selection criteria for treatment	Treatment regime	Response rate	Survival outcome	Toxicity
		Total	N+ M0						
								ILND 54% Surveillance 50%	Fibrosis/skin changes 60% ILND: Lymphoedema 44% Flap necrosis 25%
Primary CRT									
Pond 2014 [31]	RS	26	21	Stage II–IV	Concurrent RT + CT without prior surgery	CSP-based 92% 40–60 Gy 62% >60 Gy 19%	NR	1-yr OS (M0): 37% 1-yr PFS (M0): 21%	NR
McComas 2020 [108]	PS	6	6	cT1–4 N2–3 M0	Refused/ineligible for ILND	Pt/MMC or MMC/5FU + 42–57 Gy	NR	2-yr OS: 67% 5-yr OS: 44%	Lymphoedema 0%

RS = retrospective study; MCRS = multicentre RS; NRRS = nonrandomised registration study; PS = prospective study; CT = chemotherapy; RT = radiotherapy; ACT = adjuvant CT; ICT = induction CT; NACT = neoadjuvant CT; CRT = chemoradiotherapy; LN = lymph node; ILN = inguinal LN; ILND = ILN dissection; SCC = squamous cell carcinoma; Pt = platinum; CSP = cisplatin; MMC = mitomycin C; 5FU = 5-fluorouracil; TIP = taxane, ifosfamide, and Pt; TPF = taxane, Pt, and 5-flurouracil; PF = Pt and 5-FU; BMP = bleomycin, methotrexate, and Pt; VBM = vincristine, bleomycin, and methotrexate; OS = overall survival; PFS = progression-free survival; DFS = disease-free survival; G = grade; CPs = complications; AEs = adverse events; NR = not reported.
[a] Regression tree analysis to define ICT eligibility.

Eleven studies (410 patients) included in this analysis [13–15,33–40] enrolled 304 patients treated with combinations containing at least a taxane and a platinum-based drug, and 106 were treated with nontaxane-platinum regimens (Table 2). It is evident that this approach not only depends on chemotherapy but also impacts the feasibility and quality of subsequent surgical consolidation.

Although mostly cN3 cases were treated with NACT, pooled results for cN1–3 demonstrate 5-yr OS of 29% (95% confidence interval [CI] 17–37%), a pathological complete response rate of 13% (95% CI 6.6–16%), an objective response rate of 51% (95% CI 41–57%), a grade ≥3 toxicity rate of 51% (95% CI 30–72%), a toxicity-related discontinuation rate of 13% (95% CI 2.8–23%), and chemotherapy-related mortality of 4.0% (95% CI 0.41–8.4%). Subgroup analysis of responders versus nonresponders revealed a significant difference in 5-yr OS (57% vs 3.3%; $p < 0.01$). Comparison of taxane-platinum versus non-taxane-platinum regimens revealed objective response rates of 48% versus 50%, grade ≥3 toxicity rates of 55% versus 40%, and 5-yr OS rates of 29% versus 26%. There remains little evidence of survival improvements with NACT in N1–2 disease. However, in inguinal cN3 disease not immediately surgically resectable, NACT may induce a response rate to allow subsequent ILND. A multivariate model identified visceral metastases and poor performance status to be associated with unfavourable survival outcomes [47].

3.4.1.3.2. Neoadjuvant/primary RT. Studies using neoadjuvant RT for inguinal LN disease are limited. One neoadjuvant inguinal RT cohort (n = 45) was identified [28]. Of those with mobile nodes ≥4 cm in size, 18% experienced a complete or partial response to RT and the 5-yr RFS was 70% with subsequent ILND. Among those with fixed nodes, only 50% subsequently underwent ILND, with 5-yr RFS of 17%.

Three RT studies [25,60,108] on primary treatment for LN-positive nonmetastatic disease, either alone or in a CRT protocol, were included. Only limited data are available in this setting and are summarised in Table 2.

3.4.1.4. Adjuvant treatment.

3.4.1.4.1. ART. Fourteen studies reported on ART [7–10,20–27,29,74]. Most were retrospective and heterogeneous in selection, comparators, and outcome measures (Table 3). Adjuvant treatment was predominantly used in pN2–3 disease at the radiotherapist's discretion, although two studies included pN1 cases [22,29]. Doses of 45–57 Gy were administered to inguinal or inguinopelvic fields. Four studies compared ART with ACT or no adjuvant treatment [8,9,27,29]. Three studies reported survival for RT-treated patients, including adjuvant groups [22,25,28]. One reported on the use of ART in pN3 disease [20]. The remaining studies reported on contemporary management of inguinal LN disease, including ART [10,15,23,24,26]. Outcome measures varied, but most reported rates of locoregional recurrence or survival (OS or CSS).

A National Cancer Database review of outcomes noted a survival benefit with ART that was apparent in pN2 but not in pN1 disease [29]. Some patients in both groups received adjuvant or neoadjuvant chemotherapy. In 45 patients with

Table 3 – Studies on adjuvant treatment

Study by ATx type	Design	Patients (*n*)		Characteristics	ATx selection criteria	Intervention vs comparison	Recurrence	Survival outcome	Toxicity
		Total	ATx						
ART									
Jaipuria 2020 [8]	PRGS	45	25	T1–4, N2–3, M0	N2–3 after ILND with negative pelvic nodes	ACT vs ART (45–54 Gy): 45 Gy basic 54 Gy for ENE 57–60 Gy for macroscopic disease	NR	Estimated average OS: ART 47 mo ACT 33 mo ($p < 0.01$) Average OS 1007 d less with ACT ($p < 0.001$)	ART: Lymphoedema 39% Skin necrosis 0% ACT: Lymphoedema 21% HC 14% Myelosupression 7%
Johnstone 2019 [27]	MCRS	93	58	T1–4, N3 M0	ENE or >2 nodes positive after ILND (inguinal field ART) Pelvic node positive after PLND (pelvic field ART)	ART (50 Gy) vs no ART	Local recurrence ENE + ART 82% ENE w/o ART 80% No ENE + ART 50% No ENE w/o ART 17% ($p > 0.1$)	HR for OS in no ENE + IPF ART: 0.04 ($p < 0.01$) No survival benefit in ENE with ART HR for DSS in ENE with IPF ART: 0.48 ($p = 0.04$)	NR
Necchi 2019 [15]	MCRS	689	74	NR	Oncologist discretion	ART vs no ART	HR for RFS for ART 0.93	HR for OS for ART 0.99 5-yr OS with inguinal pN3: ART 52%, no ART 46%	NR
Winters 2018 [29]	RS (NCDB)	589	136	T1–3, N1–2 M0	Oncologist discretion	ART (45 Gy + boost to involved areas) vs no ART	NR	HR for OS: All ART 0.58 ($p < 0.05$) N1 ART 1.36 N2 ART 0.53 ($p < 0.05$) 5-yr OS: ART 64%, no ART 57%	NR
Tang 2017 [9]	MCRS	92	40	Pelvic node positive after PLND	Oncologist discretion	ART (mostly 50 Gy, 13% >50 Gy) vs no ART	Median time to recurrence: 7.7 vs 5.3 mo ($p < 0.05$) No ART: HR for recurrence 1.9 ($p < 0.05$)	Median OS: 12 vs 8 mo ($p < 0.05$) Median DSS: 14 vs 8 mo ($p = 0.02$) No ART: HR for OS 1.7 ($p < 0.05$)	NR
Franks 2011 [25]	RS	23	14	N2–3 M0 disease	Inguinal pN2/3 or ENE after ILND	ART 45 Gy in 20 fractions ± 12 Gy in 5 fractions	LR 43% (6/14)	3-yr OS: ART 66% ENE + 80%, ENE$^-$ 32% ($p = 0.1$)	Early skin toxicity 86% Lymphoedema 27% Groin fibrosis 22% GI toxicity 4.5%
Ager 2021 [20]	MCRS	146	125	T1–4, N3	Inguinal or pelvic ENE	ART 45 Gy in 20 fractions or 54 Gy in 25 fractions	5-yr RFS 51% LR: >50 Gy 14% <50 Gy 32% ($p = 0.13$)	5-yr-OS: 44% 5-yr CSS: 51%	NR
Chen 2004 [21]	RS	45	9	T1–4, pN3	N+ after ILND	No ART vs ART 54 Gy (40–70 Gy)	RRC: 60% vs 11% Distant: 20% vs 22%	5-yr OS: 22% 3-yr OS: 35% 1-yr OS 68%	No ART: Lymphoedema 40% Infection 20% Necrosis 0% ART: Lymphoedema 44% Infection 0% Necrosis 11%
Bandini 2021 [7]	MCRS	49	40	T1–4, pN1–3	Oncologist discretion	–	NR	5-yr OS: HPV$^\pm$ 70%, HPV$^-$ 30% ($p = 0.015$)	NR
Delannes 1992 [22]	RS	51	8	T1–3, N1-2	N+ after ILND	ART 55–60 Gy	NR	OS: 5-yr 0%, 1-yr 62%	Lymphoedema 20%

(*continued on next page*)

Table 3 (*continued*)

Study by ATx type	Design	Patients (*n*)		Characteristics	ATx selection criteria	Intervention vs comparison	Recurrence	Survival outcome	Toxicity
		Total	ATx						
								CSS: 5-yr 0%, 1-yr 62%	
Demkow 1999 [23]	RS	64	12	T1-4, N+	ENE or >2 nodes positive after ILND	–	NR	OS: 16.7%	NR
Djajadiningrat 2014 [24]	RS	944	133	T1–4, N+	≥2 nodes positive after ILND Pelvic node positive after PLND	ART 50 Gy (treated 1956–2012)	NR	5-yr CSS: N2: 66% N3: 40%	NR
Graafland 2011 [26]	RS	161	67	T1–4, N+	ENE or >2 nodes after ILND	ART 50 Gy	5-yr RFS: 16.4%	NR	NR
Ravi 1994 [28]	RS	285	12	T1–4, N+	ENE	ART 40 Gy	5-yr RFS: 8.3%	5-yr CSS: 8%	NR
ACRT									
Choo 2020 [11]	RS	23	11	T1-3 N1-3 M0	Not stated	Surveillance or ACRT (Pt-based CT; mean 56 Gy) ENE (45% vs 17%) and pN3 (72% vs 17%) more frequent in the ACRT cohort	LR: ACRT 55%, surveillance 50% ($p > 0.1$) Distant metastasis ACRT 64%, surveillance 50% ($p > 0.1$)	1-yr and 2-yr OS: ACRT 55% and 27% Surveillance 57% and 28% ($p > 0.1$) 1-yr and 2-yr CSS: ACRT 73% and 55% Surveillance 57% and 28% ($p > 0.1$) No survival difference despite higher ENE/pN3	Rehospitalisation: ACRT 64%, surveillance 17% ($p<0.05$) Systemic complication ACRT 73%, surveillance 0 ($p<0.01$)
Jaipuria 2020 [8]	PRGS	93	6	T1-4, N2-3, M0	Positive pelvic node after PLND	ACT or ACRT (50 Gy and TIP/TP)	NR	Estimated average OS: ACRT 15 mo ACT 16 mo ($p > 0.1$)	HC 14% Lymphoedema: ART 39%, ACT 14%
Maibom 2020 [30]	RS	21	21	T1-4, N3 M0	ENE after ILND *No PLND*	50–64 Gy and Pt-based CT	Disease progression 48%	Median OS: 84 mo 5-yr OS 57%	NR
Li 2021 [12]	MCRS	93	32	T1-4 N3 M0	ENE after ILND PLND: NR	ACRT (Pt-based or VBM) or ACRT (30–68 Gy)	NR	3-yr DSS: ACRT 29% ACT 16% ($p < 0.05$)	NR
Yuan 2018 [111]	RS	51	14 (7 $HPV^{\pm}$)	T1–4 N0–3 M0 and HPV status documented	NR All receiving ACRT had N1–3 disease	ACRT vs no ACRT but N+	2-yr LR rate in pN+ 46% vs 87% ($p < 0.05$) ACRT: $HPV^{\pm}$ 17% ACRT: HPV^{-} 62% ($p < 0.05$)	No difference in OS or PFS with ACRT	≥G3: 0% G2: 20% Skin toxicity: 18% vs 3% GU toxicity: 6%, vs 0% GI toxicity: 12% vs 0% Haematological toxicity: 12% vs 3%
Chen 2020 [10]	CRS (SEER)	294	96	T1–4 N0–3 M0–1	Institution-specific	ACT vs ACRT	NR	2-yr CSS: ACRT 53%, ACT 56% 2-yr CSS in N3 ACRT 51%, ACT 24%*	NR
Khurud 2022 [110]	CRS	128	102	T1–4 N3 M0	pN3	No Tx or ACT (91% TP) or ART (45–50 Gy) or ACRT	Recurrence: No Tx 87% ART 50% ACT 49% ACRT 44% RRC: No Tx 50% ART 25% ACT 25% ACRT 17%*	2yr OS: No Tx 28% ART 81% ACT 57% ACRT 75% HR for OS vs no Tx: ACT or ART HR = 3* ACRT HR = 3.1*	Lymphoedema 50% with ART

Table 3 (*continued*)

Study by ATx type	Design	Patients (*n*)		Characteristics	ATx selection criteria	Intervention vs comparison	Recurrence	Survival outcome	Toxicity
		Total	ATx						
ACT									
Necchi 2019 [15]	MCRS	689	171	T1–4 N1–3 M0	Institution-specific	ACT vs no ACT	HR for RFS 0.88 (ACT vs no ACT)	5-yr OS: pN1–2: 69% vs 66% pN3: 45% vs 38% Inguinal pN3: 52% vs 45% Pelvic pN3: 49% vs 18% (p = 0.04)	NR
Necchi 2017 [13]	MCRS	201	78	T1–4 N0–3 M0	NR	ICT or ACT or ICT + ACT	Median RFS: ACT 33 mo ICT 7.7 mo ICT + ACT 11 mo 2-yr RFS: ACT 51% ICT 23% ICT + ACT 28% (p < 0.05)	Median OS: ACT 105 mo ICT 17 mo ICT + ACT 18.5 mo 2-yr OS: ACT 57% ICT 36% ICT + ACT 32% (p > 0.05)	G3–4: 21%
Necchi 2016 [44]	RS	21	21	Tx N0–3 M0	NR	TPF	NR	1-yr DFS 55% 1-yr OS 85%	G3–4: 24%
Nicolai 2016 [14]	RS	47	19	T1–4 N2–3 M0	≥pN2 after ILND	TPF	Relapse 42%	Median OS: 15 mo 2-yr OS 45%	≥G3 AEs: 53%
Sharma 2015 [17]	MCRS	84	36	T1–4 N3 M0	Positive pelvic node after PLND	Centre-dependent	Local 2.3% RRC 20% Distant 24%	Median OS: ACT 22 mo No ACT 10 mo HR 0.4; p < 0.05	NR
Noronha 2012 [46]	RS	19	19	T1–3 N1–3 M0	pN2–3 or R1 after ILND or PLND	Taxane + Pt	LR 32%	Median DFS: 16 mo	Mortality: 5% G3–4: 37%

RS = retrospective study; CRS = comparative RS; MCRS = multicentre RS; PRGS = prospective register study; NCDB = National Cancer Data Base; SEER = Surveillance, Epidemiology and End Results; ENE = extranodal extension; CT = chemotherapy; ICT = induction CT; Tx = treatment; ATx = adjuvant Tx; ACT = adjuvant CT; ART = adjuvant radiotherapy; ACRT = adjuvant chemoradiotherapy; Pt = platinum; TPF = taxane, Pt, and 5-flurouracil; PF = Pt and 5-flurouracil; TIP = taxane, ifosfamide, and Pt; BMP = bleomycin, methotrexate, and Pt; VBM = vincristine, bleomycin, and methotrexate; w/o = without; ORR = objective response rate; pCR = pathological complete response; LR =locoregional recurrence; RRC = regional recurrence; ILND = inguinal lymph node dissection; PLND = pelvic lymph node dissection; HPV = human papillomavirus; NR = not reported; IPF = inguinopelvic field; OS = overall survival; CSS = cancer-specific survival; DSS = disease-specific survival; RFS = recurrence-free survival; DFS = disease-free survival; HR = hazard ratio; G = grade; GI = gastrointestinal; GU = genitourinary; AE = adverse events; HC = haemorrhagic cystitis.

pN2–3 disease receiving ART or ACT, the estimated OS favoured ART (47 vs 33 mo; $p < 0.0001$) [8]. Ager et al. [20] assessed 5-yr OS with ART in pN3 disease and found no significant difference with or without chemosensitisation (32% vs 54%; $p = 0.065$). There is low-quality evidence from one small cohort study suggesting a hypothesis that inguinal ART may have superior 5-yr OS in human papillomavirus (HPV)-positive than in HPV-negative cancers (70% vs 30%; HR 0.2), which will need to be substantiated in future studies [7].

3.4.1.4.2. ACT. Six studies used ACT after LND [13–15,17,44,46]. The largest published series included cohorts of patients receiving ACT, NACT, or NACT + ACT [13]. Patient selection and the chemotherapy regime varied between centres. Most patients had pN2–3 disease (83%) with bilateral inguinal involvement (43%). The chemotherapy regimen comprised taxane-platinum-5-fluorouracil (FU) or platinum-5FU in 75% of cases. Outcomes favoured ACT, with nonsignificantly longer OS and significantly longer RFS. This may be because of more cN3 cases in the NACT cohort (48% vs 24%), although 55% of the ACT group were upstaged after LND. Addition of RT, given to 36% of the ACT cohort, showed no survival or recurrence benefit. There was no difference between chemotherapy regimens, but the numbers were small. The incidence of grade 3–4 toxicity was lower with ACT than with NACT or NACT + ACT (21% vs 57% vs 100%).

In a cohort of 47 patients treated with NACT (for cN3 disease) or ACT (≥pN2 after LND) using TPF, the ACT group had a higher proportion of patients with pelvic involvement (58%) and ENE (74%) [14]. However, neither OS nor RFS significantly differed. Toxicity was lower with ACT (grade ≥3: 53% vs 85%).

The putative efficacy of ACT was reported in a large multicentre retrospective study for various chemotherapy regimens, including adjuvant use ($n = 171$) [15]. Nomogram development for OS revealed an advantage in N3 disease with both NACT and ACT, although the advantage was not statistically significant. Use of ACT in pN1–2 disease did not improve survival outcomes.

Assessment of prognostic factors affecting survival in patients receiving ACT (≥pN2 in >90%) revealed 12-mo OS of 85% [109]. On multivariable analysis, only p53 expression was associated with a nonsignificant fourfold increase in mortality.

3.4.1.4.3. ACRT. Seven retrospective studies used ACRT, usually in pN3 disease (either ENE or pelvic involvement). RT doses were similar, but chemotherapy regimens differed even within the studies themselves.

Comparison of ACRT versus surveillance in a group of 23 patients after surgery showed no significant difference in recurrence, OS, or CSS; however, pN3 rates were significantly higher in the ACRT group (73% vs 17%) [11]. Readmission and systemic complication rates were higher with ACRT.

Three studies reported ACRT for ENE after ILND [12,30,110]. Using ACRT instead of PLND for treatment of ENE after ILND, a Danish group reported favourable survival in pN3 disease (median OS 84 mo; 5-yr OS 57%) without a comparator group [30]. A multicentre study reported better DSS in ENE with ACRT in comparison to ACT (3-yr DSS 29% vs 16%; $p < 0.05$) [12]. In a single-institution study analysing adjuvant treatment in pN3, ART, ACT, and ACRT all showed better RFS and OS in comparison to no adjuvant treatment [110] and significant OS improvements were observed for either ART or ACT (HR 3.0; $p < 0.001$) and for ACRT (HR 3.1; $p < 0.001$) in comparison to no adjuvant treatment. Univariate analysis for those with only positive inguinal LNs showed that no adjuvant treatment was inferior to ACT (HR 0.2; $p = 0.008$) and ART (HR 0.2; $p = 0.005$) for OS; however, ACRT was not superior to single-modality treatment (HR 1.2).

A SEER database analysis comparing the effectiveness of ACRT and ACT showed no OS benefit with ACRT [10]. Subgroup analyses demonstrated an OS benefit in N3 disease with ACRT (2-yr CSS 51% vs 24%; HR 0.54) but no benefit in N0–2 disease.

A study examining the influence of HPV status on ACRT showed no improvement in either OS or progression-free survival in a cohort including patients with pN1–2 disease [111]. However, locoregional control was improved by ACRT or HPV-positive status, with ACRT in HPV-positive patients showing the lowest recurrence rate.

3.4.1.4.4. Complications of adjuvant therapy. Four studies described complications of adjuvant treatments [8,11,25,108]. Skin toxicity (86%) was the commonest acute side effect of ART [25], while lymphoedema rates of 50% have been reported [110]. Postoperative long-term lymphoedema was higher with ART than with chemotherapy (39% vs 21%) [8]; however, lymphoedema was not observed with primary CRT [108]. Notably, Choo et al. [11] reported high rates of rehospitalisation (64%) and systemic complications (72%) with ACRT.

3.4.2. Management of pelvic LN disease

Pelvic LN (PLN) metastases follow inguinal LN spread and are associated with worse prognosis (5-yr DSS 17% vs 62%) in comparison to cases without PLN metastases [52]. The presence of ENE and the number of positive inguinal LNs were predictive of ipsilateral PLN metastasis (0–6.5% for 1–2 LNs vs 33–67% for ≥3 LNs) [52–54]. Multivariable analysis showed that OS is worse for patients with bilateral PLN disease than for those with unilateral involvement, and the number of positive PLNs is a predictor of poor survival [19,52,57]. The presence of four or more bilateral positive inguinal LNs was the only independent predictor of bilateral PLN metastasis (OR 14.0, 95% CI 1.7–115) [57]. However, p53 immunoreactivity, LN density >30%, and primary tumour grade were additional predictors of PLN involvement [53,72].

3.4.2.1. PLND. Bilateral PLND after ILND was associated with superior 3-yr DSS to ILND alone for pN2–N3 disease after propensity score matching to adjust for potential confounders (56% vs 34%) [18]. Notably, for patients with pN2 disease, 3-yr CSS was significantly better with PLND (83% vs 50%; $p = 0.03$). This difference was not evident in a group with inguinal ENE (39% vs 25%; $p = 0.40$). Chipollini et al. [84] reported that removal of nine or more PLNs during PLND improved 5-yr OS (64% vs 47%) and 5-yr CSS (60% vs 43%) [84]. Although no suitable minimally invasive PLND studies were identified, its feasibility and safety have been demonstrated for other malignancies.

3.4.2.2. Adjuvant treatment.

3.4.2.2.1. ART. Three studies reporting on ART following PLND [9,24,27] showed a prolonged time to recurrence (7.7 vs 5.3 mo) and better median OS (12 vs 8 mo) in comparison to no ART.

A separate review of 93 patients with N3 disease compared ART after ILND and PLND to a cohort without ART, focusing on ENE presence [27]. A survival benefit was observed among patients without ENE undergoing ART (HR 0.04, 95% CI 0.007–0.62; $p = 0.037$) and a similar benefit was observed with chemotherapy (HR 0.07, 95% CI 0.006–0.86; $p = 0.038$). ART in ENE improved RFS (HR 0.48, 95% CI 0.24–0.97) but not OS at median follow-up of 9.4 mo. This suggests that ART may offer better RFS and OS in pN3 after PLND, particularly in the absence of ENE.

3.4.2.2.2. ACT. One study tested the efficacy of ACT in PLN metastasis after PLND [17]. The ACT group had more frequent inguinal (86%) and pelvic ENE (67%) but less frequent bilateral disease than a control group that more frequently received ART (50% vs 11%). Despite higher ENE, significantly higher median OS was observed with ACT (22 vs 10 mo; HR 0.40), whereas ART was not associated with a survival benefit.

A retrospective single-centre study analysing the efficacy of adjuvant taxane-cisplatin-5FU in patients with pN2–3 disease reported 2-yr RFS of 38% [14]. Interestingly, ACT resulted in longer RFS intervals in comparison to NACT with PLND. A multicentre retrospective review of 171 patients undergoing ACT after PLND found that the only statistically significant OS benefit of ACT was for pelvic pN3 disease rather than inguinal ENE [15].

3.4.2.2.3. ACRT. In a large multicentre retrospective study, ACRT seemed to provide an OS benefit in pN3 disease associated with ENE [15]. Jaipuria et al. [8] reviewed ACRT versus ACT for node positivity after PLND. OS estimates showed no difference in survival between ACRT and ACT (467 vs 484 d; $p = 0.20$) among 13 patients with pelvic pN3 disease. However, the incidence of lymphoedema was higher among those receiving RT.

3.5. Discussion

3.5.1. Principal findings

Surgery remains the standard for LN metastatic PeCa. Surveillance or delayed LND risks missing a curative opportunity. Open radical ILND is associated with significant wound-related morbidity and lymphoedema. Minimally invasive techniques seem feasible and may have lower wound-related complication rates. However, limited oncological outcomes have been reported and published series are predominantly based on cN0 cases; therefore, further comparative studies are needed.

(Neo)adjuvant treatment has no proven benefit in pN1 disease and is not recommended. Patients with more advanced disease are rarely cured by surgery alone, and multimodal treatment should be considered. NACT or ACT may be of benefit in pN2–3 disease but is associated with considerable toxicity. Patient selection should be based on fitness for at least three cycles of combination chemotherapy (including a taxane and cisplatin). ART may reduce the risk of recurrence and offer a survival benefit in pN2–3 disease. Furthermore, CRT may provide modest additional benefits in reducing locoregional recurrence in pN3 disease, especially in cases with HPV positivity or extranodal involvement.

After ILND, three or more positive nodes or the presence of ENE are predictors for PLN involvement and remain an indication for PLND, which improves outcomes in pN2 disease, but the benefit is less clear for pN3. Both ACT and CRT show modest improvements in recurrence and survival outcomes after PLND.

3.5.2. Implications for clinical practice

The majority of studies in this review are CSs or observational studies and thus the overall evidence quality is deemed low. For this reason, it is difficult to draw new firm recommendations; however, some themes that differ from current guidance are emerging and are worthy of discussion.

Surgery is the mainstay of treatment for LN-positive PeCa. Current guidelines suggest that minimally invasive ILND was feasible in small series, with no firm recommendations regarding its use. Our review confirmed the promise in reducing wound-related morbidity, but lymphatic complications remain an issue and more data are needed to confirm oncological safety when ILND is performed in cN+ disease. This field is likely to continue to evolve and we expect further studies recommending its use to be published, which may inform future guidelines.

Given the limited data and low-quality evidence, the optimal indication and order for multimodal treatment strategies are difficult to discern. Therefore, potential treatment strategies should be discussed by an experienced multidisciplinary team, balancing the potential benefits against toxicity. NACT should be reserved for fixed/bulky LN disease, followed by completion surgery if feasible, and can be considered in other N2–3 cases. Adjuvant therapy may provide benefit in pN2–3 disease.

A previous systematic review cautioned against the use of ART in pN3 disease [113]. This review informed the current EAU guidelines, which only recommend ART use in clinical studies. However, more recent data suggest that ART may indeed improve RFS and OS and can thus now be considered in the pN2–3 setting. Our review has demonstrated that ART can be safely used outside of clinical studies for pN2–3 disease, while minimally invasive ILND can be considered.

Current challenges regarding the use of multimodal therapies include: (1) identification of the most suitable patients and timing for chemotherapy (neoadjuvant vs adjuvant); (2) patient selection and timing for the addition of RT; and (3) better definition of the added benefit versus toxicity regarding efficacy and patient quality of life.

3.5.3. Implications for further research

Given the heterogeneous nature of the studies included, a preponderance of noncomparative data, and the small sample sizes, it is difficult to provide conclusive quantitative results for the research questions. Limited (comparative) data evaluating the role and safety of minimally invasive ILND, (neo)adjuvant chemotherapy, primary or adjuvant (chemo)radiotherapy, novel systemic therapies, and management of LN recurrence are available. This highlights

the need for high-quality comparative randomised studies, which is expected to remain a challenge in this rare disease.

The ongoing International Penile Advanced Cancer Trial (InPACT, NCT02305654) is a phase 3 trial with a Bayesian design incorporating two sequential randomisations. The aim is to recruit 200 patients with inguinal and/or pelvic metastases. The first randomisation will test the role of neoadjuvant therapies (NACT vs CRT) before ILND [114]. Following ILND, further randomisation will evaluate the oncological benefit of PLND and/or ACRT. The primary outcome measure is overall survival, with recruitment ongoing.

While InPACT may inform management of advanced PeCa, further studies in earlier-stage disease are also required to further improve early detection and oncological outcomes and reduce treatment-related morbidity.

3.5.3.1. Limitations and strengths. The rarity of PeCa precludes studies involving significant numbers of patients and homogeneous populations. Low-quality evidence, high RoB, and heterogeneity in outcome reporting mean that it is difficult to provide definitive conclusions. The widespread geographical and chronological nature of the studies included in the review results in different staging systems and protocols. Therefore, a quantitative analysis was not possible, so a qualitative synthesis of eligible studies was performed.

This review has some strengths. We used a systematic approach and followed a prespecified protocol that was ratified by the EAU methodology committee. Furthermore, the review is the result of a collaborative effort by an international multidisciplinary panel of experts in the management of PeCa, and provides an authoritative summary of all relevant published data available over the last 30 yr.

4. Conclusions

Patients with PeCa with locoregional LN involvement are best managed with ILND and PLND, where feasible. NACT remains reserved for patients presenting with fixed or bulky LNs. A qualified multidisciplinary team should consider the use of (neo)adjuvant treatment strategies for pN2/N3 disease, as sufficient data to allow clear recommendations regarding the optimal order and timing of the therapeutic modalities available are lacking.

The disparities in the use of RT, chemotherapy, and/or CRT in studies highlight the need for high-quality collaborative multinational studies. In addition, poor outcomes and toxicity associated with current therapeutic modalities underline the unmet need for novel approaches that are both effective and tolerable in patients with advanced LN disease.

Author contributions: Ashwin Sachdeva had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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