Review Article

Pelvic lymph node dissection alone versus adjuvant radiotherapy in node positive penile cancer: A systematic review

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ABSTRACT

Introduction: The management options for regional lymph nodes (LNs) in men with penile cancer include surveillance, surgery, and chemotherapy. The use of radiotherapy (RT) for nodal disease follows tradition and single-institution policies. We aimed to analyse the existing evidence regarding the management of penile cancer patients with suspected or known metastatic pelvic LNs using pelvic LN dissection (PLND) with RT versus PLND or RT alone.

Methods: A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, with no filters for language or time. The search was conducted in EMBASE, MEDLINE/PubMed, and Cochrane Library. Inclusion criteria were adult men with penile cancer and suspected metastatic pelvic LNs, undergoing PLND with or without RT or RT alone. Primary outcomes included disease-specific survival and locoregional recurrence. Secondary outcomes included overall survival and complications of therapy.

Results: A total of 552 articles were identified. Only eight retrospective studies were eligible for inclusion (including 406 patients). All studies had a high risk of bias. None of the studies reported the use of neoadjuvant RT. Indications for PLND varied but were usually two or more clinically positive inguinal nodes with or without extracapsular extension. Adjuvant RT was mainly used in positive pelvic LNs or pN2/pN3 stages. The rate of locoregional recurrence following adjuvant RT was 70%. Complications of treatment were reported in two studies only.

Conclusions: There is insufficient evidence to recommend the use of adjuvant RT following PLND in penile cancer patients. The quality of evidence is low due to the retrospective design and high risk of bias. Randomized clinical trials are required to assess the efficacy and safety of adjuvant RT and PLND.

INTRODUCTION

Penile cancer is a rare malignancy with limited evidence to guide management decisions in the advanced stages of the disease.[1] Moreover, invasive penile cancer has variable clinical presentations, which may lead to a delay in diagnosis resulting in relatively poor survival rates among men.[2,3] Surgery is the mainstay of treatment. Removing the tumor completely while preserving as much of the penis as possible is the aim of surgical treatment of the primary.[4] Radiation treatment of the primary tumor is an alternative organ-preserving approach with good results in T1-2 lesions <4 cm in diameter. It has the advantage of preserving sexual function, especially in younger patients.[2,5]

The presence of lymph node (LN) metastases is the most significant prognostic factor in patients with penile cancer.[6] Positive pelvic LNs in patients with penile cancer has long been associated with poorer outcomes, with very low 5-year survival rates of 9%–40%.[7-10] The lines of management of regional LNs include surveillance, pelvic LN

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dissection (PLND), radiotherapy (RT) and chemotherapy. The use of these options varies according to the stage of the primary tumor and LNs.[11] The use of RT for nodal disease follows tradition and single-institution policies. RT is widely used in some European countries for the management of regional nodal metastasis in penile cancer, despite the lack of data.[11]

The rarity of this entity poses a challenge for clinical investigation. There is limited clinical trial data to support guideline recommendations.[12,13] The present study analyzed the current evidence on the management of pelvic nodes in high-risk penile cancer (pelvic N0 and N+) with PLND with RT versus PLND or RT alone.

METHODS

Methodology

The protocol of this systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42021239161) on February 26, 2021. This study was exempted from ethics committee approval.

Types of studies

All study designs were included, whether observational (cohort and case – control studies) or clinical trials. Furthermore, single-arm case series was included. No restriction was placed upon publication date or language.

Types of participants

Eligible studies included adult patients who either had high risk of pelvic node involvement or known pelvic node involvement.

Types of interventions

Interventions considered were PLND with neoadjuvant or adjuvant RT (with or without concurrent chemotherapy), compared to PLND alone or RT alone.

Types of outcome measures

The primary outcomes in this review included disease-specific survival (DSS) (within 5 years of treatment) and locoregional recurrence. The secondary outcomes were overall survival (OS) (within 5 years of treatment) and complications of PLND and RT.

Exclusion criteria

We excluded studies available only as abstracts, duplicate reports, review articles, editorials, and clinical guidelines.

Electronic searches

This review was conducted according to the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions, version 6. The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[14]

The included studies were identified by searching the electronic databases of EMBASE, MEDLINE/PubMed, and Cochrane Library from inception to July 2020. No filters were used as regards the publication date of the studies or the language.

The search strategy used the following search terms: "penile cancer", "pelvic lymphadenectomy," and "radiotherapy." The controlled vocabulary search terms available for PubMed (MeSH terms) and EMBASE (EMTREE) were used during conduction of the search.

Searching other resources

Other relevant websites were searched including Google scholar and ClinicalTrials.gov, which was searched through the Cochrane Register of Studies interface. The websites were searched using the same search terms used for the databases. In addition, the reference lists of identified studies were also searched. Reference lists were manually searched for potentially relevant, eligible studies.

Data collection and analysis

The outcomes of the studied interventions were compared with no treatment or with each other. Some data were not available for comparisons.

Selection of studies

The list of identified abstracts was reviewed independently by two reviewers. For abstracts or references that were considered as potentially relevant by either reviewer, the full text articles were retrieved and reviewed by both reviewers for relevance and inclusion.

Data extraction and management

Relevant data were extracted by one reviewer. A standardized data collection sheet was used to extract the data. Afterward, the collected data were revised by supervisors to ensure consistency and clarity.

Extracted data included the following:

- Study characteristics: The study design, country, and institution where the study were conducted, dates defining the start and end of patient recruitment, and the sample size
- Patients' characteristics: Age, stage of cancer, and follow-up duration
- Data related to the intervention: Type of studied intervention (PLN dissection, RT, or combination), other received treatments (e.g., chemotherapy)
- The studied outcomes: DSS (within 5 years of treatment), locoregional recurrence (primary outcomes), OS (within 5 years of treatment), and complications of PLN dissection and RT (secondary outcomes).

Toxicity of RT was recorded as defined by the authors of the included studies.

Assessment of risk of bias in included studies

Risk of bias was assessed for each included study by two independent reviewers using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool.

RESULTS

Results of the search

The literature search yielded a total of 552 articles. After removal of duplicates, the abstracts of 480 articles were screened by two researchers, with subsequent exclusion of 466 articles that did not fulfil the eligibility criteria. The full text of the remaining 14 articles was further assessed for eligibility. Out of these 14 articles, 6 were excluded after full-text screening (outcomes were not reported for the intervention groups which are studied in this systematic review), leaving eight studies (including 313 patients) eligible for inclusion[7,15-21] [Figure 1].

Basic characteristics of the included studies

The eight studies included patients with penile cancer from 1956 to 2015. All the studies were retrospective. Two studies were multicentric,[18,20] with the remaining six single-institution studies from the United States of America,[15] India,[19] The Netherlands,[7,16] United Kingdom (UK),[17] and China.[21] None of the studies reported the use of neoadjuvant RT. The indications for PLND and adjuvant RT varied widely across the studies and even in the same study due to changing of the institutional management protocols over time.[7,20,21] In addition, the reported outcomes and their presentations differed greatly among the included studies, e.g., survival was presented in some studies as OS and in others as DSS, and at different time points (at 1, 3, or 5 years) [Table 1].

Assessment of risk of bias in the included studies

The risk of bias was assessed for each of the included studies. None of the studies had an *a priori* protocol. The number of patients who received PLND or adjuvant RT were not clear in three papers.[7,18] In most of the studies, the reporting of outcomes was poor, including disease-free survival (DFS),[7,15,16,18-21] complications of PLND or RT,[7,15,17-21] recurrence,[7,15,16,18,19,21] and mortality.[7,15,16,18,19,21] Overall, the included studies had a high risk of bias in most domains.

Reported effectiveness and safety of pelvic lymph node dissection with or without adjuvant radiotherapy or radiotherapy alone in the included studies

The indications for each treatment modality and the numbers receiving each treatment are listed in Table 2. The outcomes of treatment modalities as reported by the eight studies are demonstrated in Table 3. The first study was by Assimos and Jarow,[15] which was a case series reporting on three patients with moderately well differentiated, invasive squamous cell carcinoma (SCC) of the penis. The primary tumor was treated with radical penectomy. The patients had clinically positive inguinal lymphadenopathy. The median age of the patients was 62 years (range: 57-64 years). The three patients underwent laparoscopic PLND without encountering intraoperative or postoperative complications. Two patients underwent subsequent bilateral radical groin dissections, while one patient underwent a unilateral procedure. The three patients developed mild lower extremity lymphedema, which resolved with diuretic therapy and the utilization of

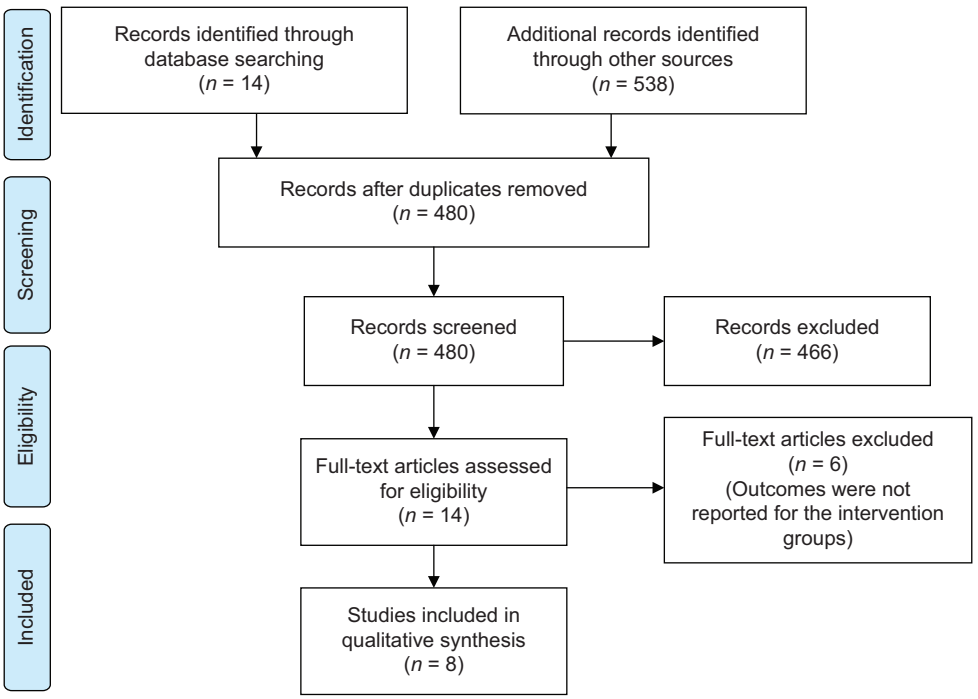

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the review

Table 1: Basic characteristics of the included studies

First author	Publication date	Country	Study dates	Study design	Patients (total number)	Median follow-up (range), months
Assimos	1994	US	Not defined	Case series	3	10 (5-18)
Ravi	1994	India	1959-1988	Retrospective cohort	285	83 (2-377)
Lont	2007	The Netherlands	1956-2001	Retrospective cohort	308	85 (25-545)
Franks	2011	UK	2002-2008	Case series	23	27 (8-84)
Djajadiningrat	2015	The Netherlands	2001-2012	Retrospective cohort	79	59 (40-72)
Li	2016	China	2000-2015	Retrospective cohort	190	Mean±SD: 21.5±23.3
Tang	2017	The Netherlands, Italy, China, Finland	1980-2013	Retrospective cohort	92	9.3 (5.2-19.8)
Johnstone	2019	Italy, The Netherlands, China, USA	Not defined	Retrospective cohort	93	9.4 (5.4-19.4)

SD: Standard deviation

Table 2: Criteria for management and numbers of patients in each treatment modality

First author	Publication date	Criteria for PLND	Criteria for ART	N undergoing PLND	N receiving ART	Chemotherapy
Assimos	1994	Persistent palpable inguinal adenopathy	-	3	-	None
Ravi	1994	NR	Tumour-positive pelvic LNs	NR	22	None
Lont	2007	≥2 tumour-positive inguinal LNs	Tumour-positive pelvic LNs	18	35	NR
Franks	2011	-	pN2/3 on inguinal LND and/or ECS	-	14	NR
Djajadiningrat	2015	≥2 tumour-positive and/or ECS in inguinal LNs	Tumour-positive pelvic LNs	50	10	NR
Li	2016	Before 2009: Solitary pelvic metastasis. Since 2009: ≥2 tumor positive inguinal LNs, ECS, or suspicious pelvic imaging	pN2 or pN3 stages	60	9	Adjuvant: 33 (28 LND, 5 PLND+ART)
Tang	2017	Before 2008, indications were not uniform across centers after 2008, ≥2 tumor positive or ECS in inguinal LNs	Positive surgical margins or pelvic ECS	52	40	None: 65 (35 PLND, 30 ART) Neoadjuvant: 14 (8 PLND, 6 ART) Adjuvant: 13 (9 PLND, 4 ART)
Johnstone	2019	≥2 tumour-positive inguinal LNs, ECS, or suspicious pelvic imaging	Tumour-positive pelvic LNs	NR	NR	None: 47 Neoadjuvant: 14 Adjuvant: 32

ART=Adjuvant radiotherapy, NR=Data were not presented, PLND=Pelvic lymph node dissection, LNs=Lymph nodes, ECS=Extracapsular spread

Table 3: Reported outcomes in the included studies

First author	Publication date	Regional recurrence following PLND alone, *n* (%)	Regional recurrence following RT, *n* (%)	DFS following PLND alone (months)	DFS following RT (months)	OS following PLND alone (time point years)	OS following RT (time point years)
Assimos	1994	1 (33)	-	NR	-	NR	NR
Ravi	1994	NR	NR	NR	NR	NR	0% (5)
Lont	2007	NR	NR	NR	NR	NR	NR
Franks	2011		6 (42.9)	-	NR	-	66% (3) 49.5% (5)
Djajadiningrat	2015	NR	NR	NR	NR	NR	NR
Li	2016	NR	NR	NR	NR	NR	NR
Tang	2017	41 (42.9)	28 (70.0)	5.3	7.7	12.7% (3)	25.5% (3)
Johnstone	2019	NR	NR	NR	NR	NR	NR

DFS=Disease-free survival, NR=Data were not recorded, OS=Overall survival, PLND=Pelvic lymph node dissection, RT=Radiotherapy

support stockings. Pathological assessment of pelvic LNs was negative, whereas examination of inguinal LNs showed one patient to be pN0, and the other two patients to be pN1. None received RT or chemotherapy. Recurrent disease developed only in one patient in the right groin. Patients were followed up for a median duration of 10 months (range: 5 – 18 months).

A retrospective cohort study was published by Ravi *et al.*,[15] which included 285 patients with penile cancer treated during the period from 1959 to 1998 (median follow-up: 83 months, range: 2-377 months) in a single institution in India. This cohort included 120 clinically node-negative patients, 129 with clinically positive inguinal LNs, and nine with distant metastases. The intervention for the primary tumour was RT. Among this cohort, 22 patients received postoperative pelvic RT (dose 40-45 Gy/4-5 weeks), including para-aortic RT (dose 40 Gy/4 weeks) in four patients, for positive pelvic (obturator, iliac) nodes on lymphadenectomy. It was not possible to ascertain the

number of patients who underwent PLND, and outcome data were not presented for this subset of patients. None of the patients who received postoperative pelvic and/or para-aortic RT for positive pelvic nodes survived 5 years.

Lont *et al.*[7] reported on a retrospective cohort, which included 308 patients with penile cancer admitted to a single institution in the Netherlands during the period from 1956 to 2001 (median follow-up: 85 months, range: 25-545 months). The cohort included 239 cases with clinically negative inguinal nodes while 69 cases had clinically positive inguinal nodes. Ipsilateral PLND was indicated in cases with involvement of 2 or more inguinal LNs. Adjuvant RT to the ipsilateral pelvic region was indicated in cases with tumour-positive pelvic LNs (dose 40-60 Gy). A total of 18 patients underwent ILND and PLND without RT. Adjuvant RT to the pelvic region following PLND was received in 35 patients. The exact survival data for patients who underwent PLND alone or received RT after PLND were not presented in the paper. However, they stated that PLND is unnecessary in stages pN0 and pN1. On the other hand, they advised that PLND should be performed in stage pN2 and that PLND alone or in combination with adjuvant RT was not sufficient for disease control in pN2 and pN3 cases. Mild to moderate lymphedema was encountered in 11/18 patients who underwent both ILND and PLND without RT. Meanwhile, mild to moderate and severe lymphedema were seen in 22/35 and 7/35 patients, respectively, in patients who underwent both ILND and PLND combined with RT.

Franks *et al.*[17] described a case-series of 23 men with penile cancer who were treated in a single institution in UK during the period from 2002 to 2008 (median follow-up: 27 months, range: 8-84 months). Fourteen patients received RT to the inguinal and pelvic regions (dose: 45 Gy/4 wk, with a further boost of 12 Gy/5 d if positive surgical margins or extracapsular spread [ECS]) after surgical treatment of the primary tumour and ILND for pN2/3. None of the patients underwent PLND. Among the patients who received adjuvant RT, 6/14 (42.9%) suffered locoregional relapse at 3 years: 1/6 with N1, 1/4 with N2 and 3/4 with N3 disease. The 3-year and 5-year OS were approximately 66% and 49.5%, respectively. According to LN staging, the OS at 3 years was 75.1%, 66.8%, and 50.3% in N1, N2, and N3 patients, respectively. The 5-year OS in N1 and N2 patients was the same as the 3-year OS, while none of the N3 patients survived beyond 40 months. The reported complications included acute skin toxicity, lymphedema of the scrotum/penis or lower limb (the cause of lymphedema was not ascertained if it was RT or surgery), groin telangiectasia/fibrosis, and late bowel symptoms. The authors did not report separately the complications for adjuvant RT patients and those who received palliative treatment, so it was not possible to determine the incidence for each group separately.

Djajadiningrat *et al.*[16] examined a retrospective cohort of 79 men with penile cancer who were treated between 2001 and 2012 (median follow-up was 59 months, IQR 40-72 months). Of the 79 patients, 60 cases underwent PLND and only 10/60 received adjuvant RT to the pelvic region. Prophylactic ipsilateral PLND was indicated in cases with 2 or more tumour-positive nodes and/or ECS in the inguinal specimen without clinical evidence of pelvic disease. Adjuvant RT to the pelvic region was indicated in patients with positive pelvic LNs, except for patients with impaired wound healing, poor performance status, previous RT to the pelvic region, or rapid disease progression. None of the patients received chemotherapy. The 5-year DSS rate in patients treated with tumour-positive pelvic nodes was significantly worse than those with tumour-negative pelvic nodes (17% vs. 62%, $P < 0.001$). The OS and DSS were not stated for each group of treatment. Postoperative complications were recorded in 14 patients, including wound infection, seroma and dehiscence (9 patients), pneumonia, delirium and ileus (5 patients).

Li *et al.*[21] described a retrospective cohort of 190 pN2-3 patients with penile cancer treated in a single institution in China between 2000 and 2015 (follow-up: 21.5 ± 23.3 months). Sixty-nine patients underwent PLND (pN2 = 22 and pN3 = 47), while 121 patients (pN2 = 66, pN3 = 55) did not undergo PLND. The indications for PLND before 2009 were evidence of solitary pelvic metastasis, while after 2009 the indications became presence of two or more positive inguinal LNs, ECS, or suspicious pelvic imaging. If pathological examination showed pN2 or pN3 stages, postoperative adjuvant therapies were recommended. Adjuvant RT alone was received in 4/69 patients with PLND and 11/121 patients without PLND. Adjuvant chemotherapy was received in 28/69 and 33/121 patients with and without LND, respectively. Combined adjuvant chemoradiotherapy was received in 5/69 and 4/121 patients with and without LND, respectively. Death was reported in 32 (46.4%) and 71 (58.7%) of the patients in PLND and no-PLND groups, respectively. The median survival time of all the patients was 20.8 months (interquartile range [IQR]: 13.8-27.9). The PLND group did not demonstrate higher 1-and 3-year DSS rates than the non-PLND group (65.7 and 39.0 vs. 65.4 and 39.6%, respectively, $P = 0.796$). The 5-year DSS of PLND group was 31.5% and 29.7% for the non-PLND group. The authors did not mention complications of treatment and no details were stated as regards the subgroups of treatment modality (PLND with RT and PLND alone). The outcomes were not recorded for each nodal stage separately.

Tang *et al.*[20] conducted a retrospective cohort study on 92 pN3 patients with locally advanced penile cancer who underwent ILND and PLND. The data were collected from 4 international centres from 1980 to 2013 (Median follow-up: 9.3 months, IQR: 5.2-19.8 months). This study included a subset of patients from the study by Djajadiningrat *et al.*[16]

Adjuvant RT was received in 40/92 patients (dose: 50 Gy in 27 patients, less than 40 Gy in 4 patients, more than 50 Gy in 5 patients, and unknown in 4 patients). Recurrence occurred in 41/52 and 28/40 patients without and with adjuvant RT, respectively, with no significant difference ($P = 0.32$). Deaths of cancer were 39/52 and 24/40 patients without and with adjuvant RT, respectively, with no significant difference ($P = 0.14$). The median OS for adjuvant RT was significantly longer than in nonradiated patients (12.2 vs. 8 months, $P = 0.044$). The same finding was noted as regards the median DSS (14.4 vs. 8 months, $P = 0.023$). The median time to recurrence for adjuvant RT was 7.7 months compared to 5.3 months for nonradiated patients ($P = 0.042$). On multivariable analysis, patients who did not undergo adjuvant RT were independently associated with poor OS (hazard ratio [HR] = 1.7; 95% confidence Interval [CI]: 1.01-2.92; $P = 0.04$), poor DSS (HR = 1.9; 95% CI: 1.09-3.36; $P = 0.02$), and increased recurrence hazard (HR = 1.8, 95% CI = 1.06-3.12, $P = 0.03$) after adjusting for pelvic ECS, chemotherapy, grade and treatment year.

The last study was by Johnstone *et al.*[18] who conducted a retrospective multicentre cohort study. The analysis included 93 patients with pT1-4 N3 M0 SCC of the penis (median follow-up: 9.4 months, interquartile range: 5.4-19.4 months). The dataset of patients included seems to include a subset of those included in the study by Tang *et al.*[20] PLND was indicated according to the institutional protocol, but in general the indications included the presence of two or more positive inguinal LNs, ECS, or suspicious pelvic imaging. Ipsilateral pelvic adjuvant RT was indicated for patients with positive pelvic LN (dose: 50 Gy). It was not possible to ascertain the numbers of patients who underwent PLND alone or received RT. Chemotherapy was received by 46 patients. Pelvic RT was associated with a higher OS and a reduced recurrence risk in the pelvis (HR = 0.03, 95% CI = 0.002-0.363, $P = 0.006$).

The current systematic review was unable to conduct direct comparisons between the two treatments because of the heterogeneity across the included the studies as well as the limited data that could be extracted from most of them. This limitation of the previous studies warrants further investigation by future studies of the role of adjuvant RT and PLND in node-positive penile cancer.

DISCUSSION

Summary of the results

There were wide variations in the indications of PLND and adjuvant RT across the studies. The variations existed even within the patients in the same study, either due to a multicentre nature[20] or due to changes in institutional protocols over the long-time duration specified in the study. PLND was indicated in patients with two or more tumour-positive inguinal LNs in the study by Lont *et al.*[7] The same indication was stated by Djajadiningrat *et al.*[16] and Johnstone *et al.*,[18] besides the presence of ECS. In the study by Li *et al.*,[21] PLND was indicated for solitary pelvic metastasis before 2009, while the indications included presence of two or more tumour-positive inguinal LNs, ECS, or suspicious pelvic imaging after 2009. In the study by Tang *et al.*,[20] the indications before 2008 differed among the centres, while after 2008 they became uniform and similar to those stated by Djajadiningrat *et al.*,[16] Johnstone *et al.*,[18] and Li *et al.*[21] As regards adjuvant RT, the indication was detection of tumour-positive pelvic LNs in most studies.[7,16,18,19] In the remaining studies, adjuvant RT indications included pN2/3 on ILND and/or ECS,[17] pN2 or pN3 stages,[21] and positive surgical margins or pelvic ECS.[20] These variations resulted in heterogeneity of results across the studies.

The studies by Lont *et al.*,[7] Djajadiningrat *et al.*,[16] Li *et al.*,[21] Tang *et al.*,[20] and Johnstone *et al.*[18] included groups of patients who underwent both intervention lines. However, only two studies[18,20] reported that non-irradiated pN3 patients had a worse OS and increased risk of recurrence. Moreover, Tang *et al.*[20] reported that non-radiated patients had shorter median OS, DSS, and DFS. The two studies concluded that adjuvant RT to inguinal and pelvic regions in pN3 penile cancer patients may improve regional control and survival. The remaining studies did not clearly state the outcomes for these two groups, as their focus was on other comparisons using different basis for dividing patients' groups. Meanwhile, Lont *et al.*[7] reported that PLND alone or in combination with adjuvant RT was not sufficient for disease control in penile cancer patients with pN2 and pN3 LN staging, but they did not provide enough data about the outcomes to assess their conclusion. The controversies among the results of these studies could be attributed to variations in the study design, differentiation of the tumour, and pathological variant across the different studies. The patients in the study by Lont *et al.*[7] were classified according to pathological staging of LNs; the use of adjuvant RT after PLND was not the focus of this study. In addition, the reporting of outcomes varied markedly from one study to another, which rendered pooled analysis for performance of meta-analysis impractical.

Overall, the results of the included studies are inconclusive, and the quality of evidence derived from these studies is low. Although the two studies by Tang *et al.*[20] and Johnstone *et al.*[18] reported favourable outcomes in patients who received adjuvant RT after PLND, the risk of bias was high. Additionally the study by Johnstone *et al.*[18] included a subset of the patients included by Tang *et al.*[20] In addition, the design of the two studies was retrospective, and the number of patients in both was small. Moreover, both studies did not report on toxicities and complications related to RT due to unavailability of data as they stated. Two studies only[7,17] reported on toxicities/complications related to adjuvant RT. Lont *et al.*[7] compared the rate and severity

of lymphedema following PLND alone and RT after PLND. Their results showed comparable rate of lymphedema between the two groups, but with higher grade of severity in those who received adjuvant RT. Franks *et al.*[17] reported the occurrence of acute skin toxicity in their series.

Overall completeness, applicability, and quality of the evidence

The results of this systematic review show that the available evidence on the role of PLND alone versus adjuvant RT or RT alone in node positive penile cancer patients is very limited. The evidence from the included studies is downgraded by their design (case series and retrospective cohorts) as well as the biases (under the results section) in selection of patients and reporting of outcomes [Table 4]. Moreover, the indications of adjuvant RT and PLND varied widely across the studies and even within the same study due to changing of institutional protocols of treatment over time. These variations in indications of treatment and methods of outcome measurement and reporting resulted in marked heterogeneity among the studies and did not allow conduction of pooled analysis. In addition, all the included studies, excepting that by Tang *et al.*,[20] made no direct comparisons between the two treatment modalities; hence, the current systematic review was unable to compare their efficacy or safety. Alternatively, we presented the data of each study separately in this systematic review. This highlights the need for a focused, collaborative research that addresses this gap of knowledge regarding the role of adjuvant RT combined with PLND.

As regards the use of neoadjuvant RT in node positive patients before PLND, the literature search did not yield studies that investigated this treatment modality. One of the included studies[21] compared between patients undergoing PLND and those who did not and reported the lack of significant difference in 1-and 3-year DSS rates, questioning the efficacy of PLND.

Agreements and disagreements with other studies or reviews

To date this is the first systematic review to assess the efficacy and safety of adjuvant RT and PLND in patients with penile cancer, compared with PLND alone. A systematic review by Robinson *et al.*[22] assessed the risks and benefits of adjuvant RT after ILND in node-positive penile cancer, but they did not report separately on the subset of patients who underwent adjuvant RT and PLND. They concluded that good-quality evidence was lacking to support this line of therapy, thus no evidence is present to recommend it. We found also, like them, a lack of good quality studies that assess the role of RT prior to or after PLND.

Implications for practice, policy, and future research

Based on the results of this systematic review, the efficacy of adjuvant RT following PLND in pN3 penile cancer patients, in terms of locoregional control and survival, is inconclusive. Moreover, the cumulative adverse effects which could be encountered due to adjuvant RT and PLND in such high-risk patients may outweigh the benefits, though very few reports were found on RT-related toxicities and complications in those patients. Therefore, the currently available evidence does not recommend the administration of adjuvant RT following PLND as a routine, standard clinical practice. The administration of adjuvant RT after PLND should thus presently be limited to prospective controlled clinical trials only until further evidence is obtained. A recommendation is the conduction of future prospective observational and randomized controlled clinical trials, with sufficient sample size, to assess the role of adjuvant RT after PLND in node-positive penile cancer patients. As regards PLND alone, its efficacy is questionable compared to no PLND. To confirm the effect of PLND on OS and DSS, further prospective studies, preferably randomized clinical trials, are required with patient stratification according to LN staging.

CONCLUSIONS

There is insufficient evidence to recommend the use of adjuvant RT following PLND in penile cancer patients. The quality of evidence is low due to the retrospective design and high risks of bias. The impact of PLND alone on OS and DSS needs to be confirmed and benefits should be weighed against the adverse effects. Randomized clinical trials are required to assess the efficacy and safety of RT following PLND as well as to compare PLND against no dissection, with patient stratification according to LN staging.

Additional research work is required to provide evidence that can recommend one treatment modality over the other

Table 4: Summary of findings and level of evidence

Outcome	Number of participants (number of studies)	Overall results	Quality of the evidence (GRADE)
Regional recurrence following PLND alone	55 (2)	33% to 42.9%	Low (study limitations and inconsistency)
Regional recurrence following RT	54 (2)	42.9% to 70%	Low (study limitations and inconsistency)
DFS following PLND alone (months)	52 (1)	5.3 months	Low (study limitations)
DFS following RT (months)	40 (1)	7.7 months	Low (study limitations)
OS following PLND alone	52 (1)	12.7% at 3 years	Low (study limitations)
OS following RT	76 (3)	25% to 66% (3 years) 0 to 49.5% (5 years)	Low (study limitations and inconsistency)

DFS=Disease-free survival, OS=Overall survival, PLND=Pelvic lymph node dissection, RT=Radiotherapy

among PLND, chemotherapy, RT, chemoradiotherapy, or combined surgery with adjuvant RT. The InPACT study is an international phase III clinical trial (NCT02305654) attempting to provide some evidence regarding management of patients with penile cancer and positive nodes through assessing the relative benefits and sequencing of surgery, chemotherapy, and chemoradiotherapy in adult male patients with SCC of the penis.

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