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European Association of Urology

Review – Penile Cancer

Risks and Benefits of Adjuvant Radiotherapy After Inguinal Lymphadenectomy in Node-positive Penile Cancer: A Systematic Review by the European Association of Urology Penile Cancer Guidelines Panel

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Abstract

Context: Management of men with penile squamous cell carcinoma (PSCC) who have high-risk features following radical inguinal lymphadenectomy (ILND) remains controversial. European Association of Urology guidelines state that adjuvant inguinal radiotherapy (AIRT) is "not generally recommended". Despite this, many centres continue to offer AIRT to a subset of men.
Objective: To undertake a systematic review of the evidence on AIRT in node-positive men with PSCC.
Evidence acquisition: A systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with no language or date restriction. Inclusion criteria were men with PSCC, pathologically staged inguinal node positive after ILND. The intervention included ILND with AIRT compared with ILND alone. Primary outcomes were relapse-free survival and toxicity. Risk of bias assessment was undertaken.
Evidence synthesis: A total of 913 abstracts were identified and screened independently by two reviewers. Seven studies were eligible for inclusion: six full-text manuscripts and one conference abstract. All were retrospective series and at a high risk of bias. The selected studies included 1605 men. Indications for AIRT varied but were typically involvement of two or more inguinal nodes or extranodal extension. Regional recurrence rate following AIRT was reported at 10–91.7%. Only one study reported on toxicity. Two studies compared recurrence and survival between men who received and who did not receive AIRT, with no significant difference ($p > 0.05$).
Conclusions: The evidence indicates that men treated with AIRT do not gain benefit with respect to relapse or survival. Uncertainty remains due to the retrospective nature and high risks of bias across the evidence. Given the lack of evidence supporting AIRT, it cannot be recommended for routine practice.
Patient summary: Men with penile cancer who have involvement of the inguinal lymph nodes are at a high risk of cancer recurrence and death. We reviewed the literature to see if radiation treatment after removal of the nodes provided benefit. We did not find any good-quality evidence supporting this treatment, and hence it cannot be recommended.

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1. Introduction

Penile cancer is a rare cancer in the Western World, with an overall incidence in the USA and Europe of <1.0/100 000 males. Approximately 95% of penile cancers are of squamous cell histological type, and around one-third of cases are linked to human papilloma viral carcinogenesis [1]. The peak age of diagnosis is in the 6th decade of life [2].

The presence of metastatic disease in the regional lymph nodes (LNs) at presentation has a significant impact upon prognosis. In contemporary series, the overall survival (OS) of men with penile cancer at 5 yr is >90% in the absence of LN metastases but falls to 29–51% in the presence of LN involvement, and with pN3 disease 5-yr survival rates are very low at 0–17% [3–5]. The outlook for those who develop nodal recurrence after radical inguinal lymphadenectomy (ILND) is particularly poor with a 5-yr survival rate of <40% and median survival of only 4.5 mo [6]. While the increased use of penile-preserving surgery and minimally invasive LN staging such as dynamic sentinel LN biopsy has reduced the morbidity of penile cancer treatment, the survival rates of penile cancer patients with LN disease have changed very little in the USA and Europe since the 1990s [7]. There is evidence that this may at least in part be attributable to the underutilisation of proven therapy, in particular ILND [8], rather than a lack of refinement of treatments.

Lymphatic spread of penile cancer is predictably via the inguinal and pelvic LNs, with the superficial and deep inguinal nodes being the first sites of metastatic spread [3]. LN management typically involves staging lymphadenectomy, LN sampling in the form of dynamic sentinel node biopsy (DSNB), or surveillance. Current guideline recommendations are to use adjuvant chemotherapy in LN-positive patients after ILND with proven effects on OS and cancer-specific survival (CSS) [4]. Radiotherapy of the inguinal regions has been used for the palliative treatment of LN disease and as an adjuvant treatment in high-risk LN-positive patients following ILND. However, on the basis of a lack of data supporting the use of adjuvant radiotherapy in penile squamous cell carcinoma (SCC), the European Association of Urology (EAU) guidelines [2] do not recommend adjuvant radiotherapy for the inguinal region. The guidelines suggest that adjuvant inguinal radiotherapy (AIRT) may be considered in "selected" patients with extracapsular nodal extension (ENE). Adjuvant radiotherapy in other SCC tumour sites, in particular head and neck SCC, has proven survival benefit [5]. This, combined with evidence that radiotherapy can be used to treat the primary tumour in penile cancer [6], leads to the hypothesis that AIRT following radical ILND might be able to treat residual microscopic disease, potentially reducing the incidence of regional and distant recurrence. However, this consideration does not take into account potential differences in the radiosensitivity of different histological subtypes of penile SCC.

The aim of this systematic review was to evaluate the effectiveness and toxicity of AIRT in penile cancer after radical ILND for LN-positive disease, on the basis of the published evidence.

2. Evidence acquisition

2.1. Search strategy

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. The search was conducted in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions [10]. Studies were identified by searching electronic databases and relevant websites. Highly sensitive electronic searches were conducted to identify published and ongoing studies of adjuvant radiotherapy for pN1 penile cancer. Searches were limited to studies published from 1946 onwards to May 2017, but no language restrictions were imposed (Supplementary material). The search was complemented by additional sources, including relevant systematic reviews and the reference lists of included studies, which were hand searched to identify additional potentially relevant studies. Additional reports were identified by a reference panel (EAU Penile Cancer Guidelines Panel). Independent reviewers (R.R., A.C., and T.A.) screened all abstracts and full-text articles independently. Disagreement was resolved by a third party (L.M.).

2.2. Types of study design and participants included

All study designs were included. No restriction was placed upon publication date or language. Eligible studies had to include patients with inguinal node-positive penile SCC, pathologically staged, who had received AIRT after radical ILND with curative intent. Studies containing patients treated with palliative intent or those with SCC of the urethra were not excluded, provided those patients did not represent >10% of the cohort. Although all study designs were included, single-arm case series with <10 patients were excluded. Studies including patients with non-SCC of the penis, prior inguinal or pelvic radiotherapy, or distant metastases were excluded. Neoadjuvant chemotherapy was not an exclusion criterion.

2.3. Types of interventions included

The experimental intervention was considered as radical ILND with ipsilateral AIRT, with or without concurrent chemosensitisation, in comparison with the control of radical ILND alone.

2.4. Types of outcome measures included

The primary benefit outcome was relapse-free survival (within 5 yr of treatment), and the primary harm outcome was toxicity from radiotherapy. The secondary outcomes were regional recurrence, OS and CSS at 3 and 5 yr, complications of treatment, quality of life measurements, sexual function, urinary function, chronic skin toxicity, need for salvage treatment, and time from diagnosis to treatment. There was no restriction on how toxicity was defined (ie, as defined by the authors). The predefined subgroups of

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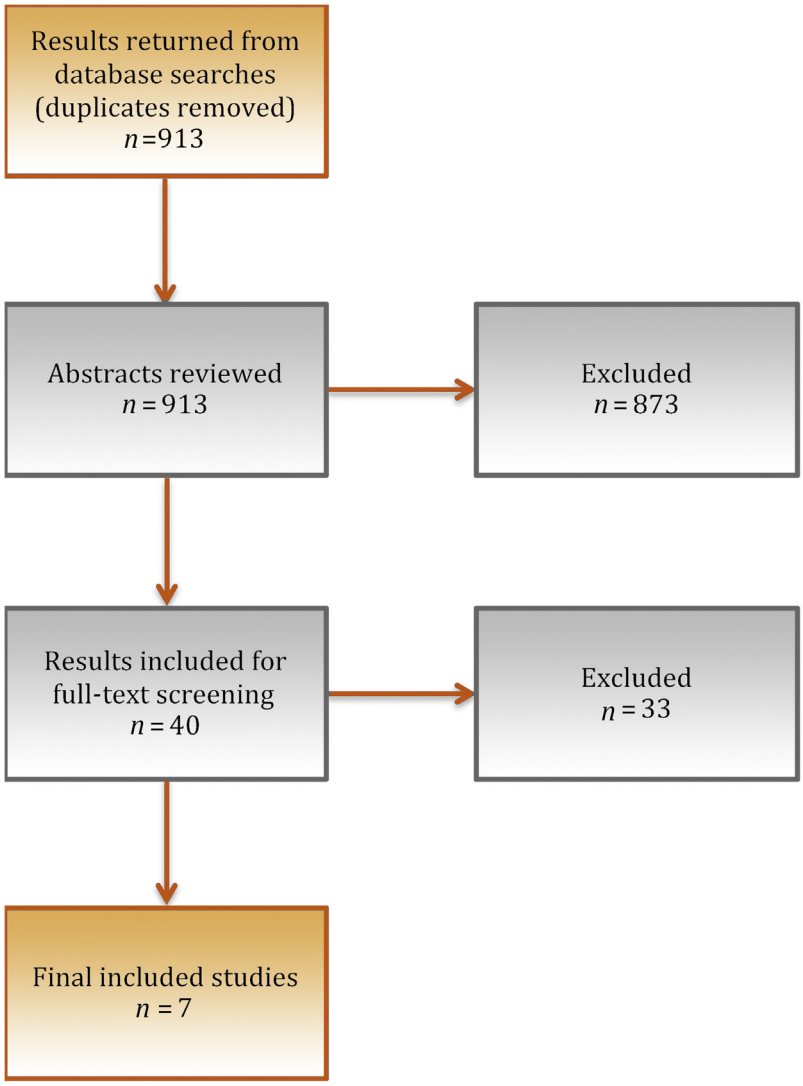

Fig. 1 – PRISMA diagram of study selection. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

interest for further analysis were patients who received additional pelvic radiotherapy compared with AIRT alone, radiation dosimetry, and chemoradiotherapy compared with radiotherapy alone, and patients with clinically positive nodal disease versus clinically negative disease at presentation.

2.5. *Data extraction*

Using a standardised form, data were extracted on the characteristics of the studies, including study design, country and institution where the data were collected, dates defining the start and end of patient recruitment and follow-up, demographic and clinical characteristics, and the defined outcome measures described above.

2.6. *Assessment of RoB risk of bias and cConfounders*

Risk of bias (RoB) in the included noncomparative series was evaluated independently by two reviewers (R.R. and L.M.). The aim of this evaluation was to determine the external validity by assessing whether study participants were selected consecutively or were representative of a wider patient population, along with attrition bias, selective outcome reporting, and whether an a priori protocol was available (indicating a prospective study design) [11].

3. Evidence synthesis

3.1. *Quantity and quality of evidence*

A total of 913 articles were identified by the literature search. Of these, 40 articles were selected for full-text screening and seven studies (including 1605 patients) were eligible for inclusion (Fig. 1) [5,6,9–13]. However, there was an overlap with respect to included patients between two of the studies [12,13], and it was not possible to determine, in all of the included studies, how many men underwent AIRT. All studies were retrospective series, six of which were published manuscripts and one was a conference abstract. In all the

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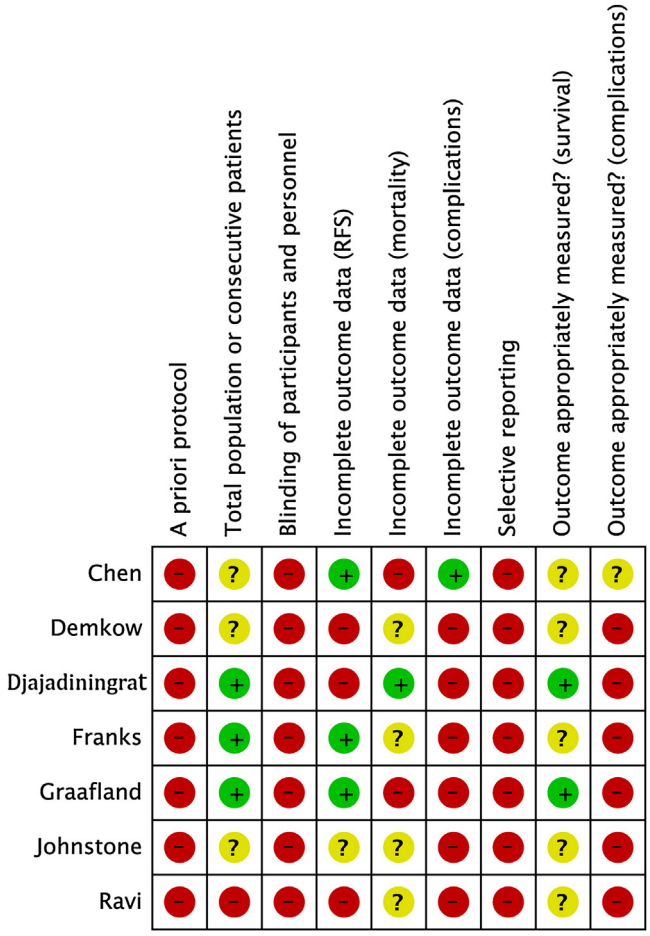

Fig. 2 – Risk of bias summary of the included studies. RFS = relapse-free survival.

included studies, the reporting of outcomes was poor, particularly with respect to treatment toxicity and long-term side effects. Overall, the studies had a high RoB (Fig. 2). None of the included studies included an a priori protocol, and the outcome data for the majority of the studies, with respect to both recurrence and survival, were limited in relation to AIRT. Only one study reported on the potential harms of AIRT.

3.2. *Baseline characteristics of included studies*

The included studies described treatment spanning 7 decades (back to 1959), and the majority of the included men were treated over 2 decades ago. There was a high level of heterogeneity with respect to indications for AIRT, radiotherapy field, dosimetry, and outcomes presented. Only one study was multicentre, with the remaining six being single-institution series from Europe (four studies), India, and Asia. The characteristics and outcomes reported in the studies are summarised in Tables 1 and 2, respectively.

3.3. *Results of clinical effectiveness and toxicity*

In the first study in 1994, Ravi et al. [14] reported retrospectively on 285 patients treated with radiotherapy for penile cancer between 1959 and 1998 (median follow-up 83 mo, range 2–377) in a single centre. This cohort included 120 clinically node-negative patients, 129 with clinically positive inguinal LNs, and nine with distant metastases. The intervention for the primary tumours was radiotherapy. Patients with clinically positive inguinal LNs <4 cm underwent ILND. Of that cohort, 12 patients underwent postoperative AIRT because of ENE (14 groins, dose not defined). Five-year disease-free survival in that cohort of 12 men was 8% (one patient).

In 1999, Demkow [15] retrospectively described a cohort of 64 patients treated in a single centre from 1989 to 1998 (median follow-up 33 mo, range 3–120). Patients with palpable nodes (persisting after 2 wk of antibiotics), primary tumours ≥T2 (independent of grade), or G3 primary tumours underwent bilateral ILND. Pelvic LN dissection was undertaken if pelvic LNs were enlarged on computed tomography. AIRT was given to men with two or more pathologically involved inguinal nodes or ENE, but only in those with negative pelvic nodes. The dose of radiotherapy was not defined. Twelve patients received AIRT, of whom 10 (83%) had died of penile cancer at 5-yr follow-up. No other outcomes were reported for the men who received AIRT.

Chen et al. [16] in 2004 published a retrospective analysis of 45 men without distant metastases, treated at a single institution between 1989 and 2000 (median follow-up 37 mo, range 6–179). Forty patients had SCC histological subtype, of whom 17 had pathologically proven inguinal LN involvement following surgical treatment of the primary tumour. Fourteen men with pathologically positive LNs underwent ILND, of whom nine received AIRT. The decision whether to give AIRT or not is not described. Radiotherapy was given 4–5 wk after surgery with a median dose of 54 Gy (range 40–70 Gy, fractionated at 1.8–2 Gy). The radiation field was described as the primary tumour, local extension sites, bilateral inguinal, and lower iliac LNs. In the 40 men with SCC, the 5-yr OS was 70% for N0 versus 22% for N+ disease ($p = 0.01$). Survival based upon further subgroups was not reported. Of those men with pathological N+ disease, local recurrence occurred in three of the five (60%) who underwent ILND alone compared with one of the nine (11%) who received adjuvant radiotherapy ($p = 0.057$). Of the entire cohort of 45 men, 10 underwent ILND alone and nine ILND and AIRT. Complications described were four in each group developing grade 2–3 lymphoedema, wound infections in two from ILND-alone group, urethral stenosis in one from the AIRT group, and one case of severe inguinal radionecrosis in the AIRT group.

The series by Franks et al. [17], published in 2011, described a retrospective single-institution cohort of 23 men with penile SCC treated with inguinal and pelvic radiotherapy between 2002 and 2008 (median follow-up 27 mo, range 8–84). In that cohort, 14 men received AIRT to the inguinal and pelvic regions after surgical treatment of the primary tumour and ILND for pN2/3 and/or ENE. No patient underwent pelvic node dissection. The radiotherapy target region included the bilateral iliac, presacral, obturator, and groin nodes, extending to the aortic bifurcation

Table 1 – Study characteristics

First author	Institution/country	Publication date	Study dates	Study design	Total number of men in study	Median follow-up (range), mo	Median age (range), yr	Treatment of primary tumour	Criteria for giving AIRT	Number of men receiving AIRT
Ravi [14]	India	1994	1959–1998	Retrospective	285	83 (2–377)	[a]	Radiotherapy	ENE	12
Demkow [15]	Poland	1999	1989–1998	Retrospective	64	33 (3–120)	64 (21–86)	Surgery	≥2 involved inguinal LN or ENE	12
Chen [16]	Taiwan	2004	1989–2000	Retrospective	45	37 (6–179)	64 (29–87)	Surgery	[a]	9
Franks [17]	UK	2011	2002–2008	Retrospective	23	27 (8–84)	58 (40–81	[a]	pN2/3 or ENE	14
Graafland [13]	The Netherlands	2011	1988–2007	Retrospective	161	60 (16–165)	64 (33–91)	Surgery	≥2 involved inguinal LN or ENE	67
Djajadiningrat [12]	The Netherlands	2014	1956–2012	Retrospective	944	64 ([a])	64 (21–96)	[a]	≥2 involved inguinal LN or ENE	[a]
Johnstone [18]	US, Italy, China, The Netherlands	2016	Not defined	Retrospective	93	9.4 (9.3–19.4 [b])	65 (36–90)	[a]	Inguinal and/or pelvic LN involvement	[a]

AIRT = adjuvant inguinal radiotherapy; ENE = extracapsular nodal extension; LN = lymph node.
[a] No data presented or data unclear.
[b] Interquartile range.

superiorly and to below the groin scar inferiorly. Patients received 45 Gy in 20 fractions over 4 wk, with a further "boost" of 12 Gy in five fractions over 5 d if required. The authors did not define the indications for a radiotherapy "boost". The median time to AIRT was 87 d. Acute skin toxicity due to radiotherapy was noted in 19 of the total of 23 men. Other side effects were poorly documented. Of the cohort of 14 men who received AIRT, six (42.9%) developed locoregional relapse at 3 yr and OS was 66%. OS at 5 yr was not given in the text, although from the Kaplan-Meier plots it can be estimated at around 50%. All deaths reported were due to penile cancer.

The 2011 series by Graafland et al. [13] is a retrospective analysis of 161 men with pN+ penile SCC treated at a single institution between 1988 and 2007 (median follow-up 60 mo, range 16–165). All men had surgical treatment of the primary tumour. If ILND confirmed metastases in two or more LNs and/or ENE, patients underwent pelvic node dissection followed by AIRT. A total of 87 groins, in 67 men, were treated with AIRT. Radiotherapy was given as 50 Gy in 25 fractions, five fractions per week. The ipsilateral pelvic nodal regions were included if pelvic nodes were confirmed to be involved by histopathology. From the overall cohort of 161 men, inguinal recurrence occurred in 26 at a median time of 5.7 mo. Of the 26, 11 had undergone AIRT and 11 developed recurrence before AIRT was commenced. In the remaining four, AIRT was not administered (due to the reporting centres' criteria for administering AIRT) as the patients had been staged as pN1.

The study included by Djajadiningrat et al. [12] is from the same institution as that by Graafland et al. [13] and incorporates the cohort from the earlier publication, examining survival in a much larger cohort of 1000 men treated for SCC penis between 1956 and 2012. Median follow-up was 66 mo in 944 included patients (56 excluded for treatment refusal or missing data). Until 1988, clinical N + (cN +) patients underwent ipsilateral ILND and clinical N0 (cN0) patients were managed by surveillance. From 1988 onwards, elective ILND was undertaken for cN0 with ≥T2 and or ≥G3 tumours. DSNB was introduced in 1994 for cN0 patients with ≥T2 tumours and from 2004 onwards for cN0 patients with ≥T1 and or ≥G2 tumours. From 2001 onwards, radical ILND was performed only in patients with histologically positive sentinel nodes. The subsequent management of histologically positive ILND was as described by Graafland et al. [13], that is, if histopathology revealed two or more positive inguinal nodes and/or ENE in the removed inguinal specimen, a subsequent ipsilateral pelvic lymphadenectomy and AIRT followed. In patients with tumour-positive pelvic nodes, irradiation to the pelvic region followed. In general, the radiotherapy dose was 50 Gy (25 fractions of 2 Gy). The authors divided the patients into four cohorts: 1956–1987, 1988–1993, 1994–2000, and 2001–2012, containing 97, 55, 164, and 628 patients, respectively (all patients treated for penile cancer, not just N +). The reported 5-yr CSS estimates were 50%, 83%, 60%, and 66% ($p = 0.52$) and 31%, 71%, 40%, and 37% ($p = 0.17$) for pN2 and pN3 patients across the four cohorts, respectively. No data on treatment side effects were

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Table 2 – Study results

First author	Publication date	Regional recurrence rate following AIRT (time point years)	OS following AIRT (time point years)	Data presented on complications
Ravi [14]	1994	91.7% (5)	[a]	No
Demkow [15]	1999	[a]	16.7% (5)	No
Chen [16]	2004	11.1% ([a])	[a]	Yes
Franks [17]	2011	42.9% (3)	66% (3) Estimated 50% (5)	No
Graafland [13]	2011	16.4% (5)	[a]	No
Djajadiningrat [12]	2014	[a]	[a]	No
Johnstone [18]	2016	With ENE 34% ([a]) Without ENE 10% ([a])	[a]	No

AIRT = adjuvant inguinal radiotherapy; ENE = extracapsular nodal extension; OS = overall survival.
[a] No data presented.

reported. The authors concluded that improved survival of cN+ patients was due to the introduction of DSNB, but no difference due to adjuvant radiotherapy could be observed.

The last study included is a conference abstract from 2016 by Johnstone et al. [18] reporting a retrospective multicentre analysis of data from four international tertiary cancer centres. The study examined the role of ENE and AIRT in men with penile cancer. The study included 93 men with a median age of 65.3 yr and a median follow-up of 9.4 mo. Of those men, 72% and 49% had ENE in the inguinal and pelvic LNs, respectively. In men with ENE, infield failure occurred in 17/50 (34%) of those who received AIRT and 10/38 (26.3%) of those who did not (p = not significant). In men without ENE (LN status not further defined in the abstract), infield recurrence occurred in five of 50 (10%) and three of 24 (12.5%) of those who received and did not receive AIRT, respectively (p = not significant). The authors further comment that AIRT was not associated with improved OS ($p = 0.073$) or reduced recurrence rate ($p = 0.492$).

3.4. Discussion

3.4.1. Principal findings

This review demonstrates that current evidence on the role of AIRT after ILND for LN-positive penile cancer is very limited. The rigorous search and review criteria applied identified only seven publications for inclusion, all of which were case series and the majority were relatively small cohorts. However, given the low incidence of penile cancer, this is not unexpected. All the evidence within this review is limited by the retrospective nature of the published series and the inherent associated referral and selection biases. There was marked variance in the indications for, the timing, target field, and dose of adjuvant radiotherapy given. These variations and the differences in outcome reporting resulted in significant heterogeneity between the series. This made direct comparisons impractical, and as such the data of each series were presented independently.

The absence of information on toxicity is disappointing, with only two of the series reporting limited data. Acute skin toxicity appears to be a common side effect, occurring in 83% of the AIRT cohort in the Franks et al's [17] series. Since the authors acknowledge that side effects were not graded, it is difficult to draw any real conclusions from these data. The survival of node-positive penile cancer patients remains very poor. In an attempt to improve survival, a number of centres have adopted the use of adjuvant treatment by radiotherapy or chemotherapy. A concern is the cumulative morbidity associated with ILND and AIRT. Consequently, some centres offer only AIRT in select cases in view of lacking data on survival benefit. This review has failed to identify robust evidence on the added toxicity of AIRT.

Regarding the most important outcomes of regional recurrence, OS, and CSS, published data are very varied. The publications by Ravi et al. [14] and Demkow [15] report poor 5-yr OS with AIRT. However, in the cohort reported by Ravi et al. [14], patients that received AIRT represented <10% of the clinically node-positive cohort, indicating a strong selection bias.

The series reported by Demkow [15], Franks et al. [17], and Djajadiningrat et al. [12] applied very similar selection criteria for the administration of AIRT. The reported outcome of the 12 patients with AIRT in the series of Demkow [15] does not support the use of AIRT. However, local tumour stages in this series were varied and included one patient with T4 disease, which may represent palliation rather than adjuvant treatment with curative intent. The series by Franks et al. [17] may contain a referral bias since some of the patients underwent surgery for the primary tumour and ILND in other institutions, and were then referred for AIRT. This might have resulted in delays that potentially could also affect treatment outcomes. In the series by Graafland et al. [13], 11 patients developed regional recurrence after radical ILND before the start of AIRT. This highlights that even when treatment is delivered in a high-volume specialist centre, the natural history of the disease may limit the use of adjuvant therapy. The large series published by Djajadiningrat et al. [12] also did not demonstrate any benefit of AIRT in node-positive patients after radical ILND. The series of Chen et al. [16] reported a low regional recurrence rate of 11% in the AIRT cohort. However, the authors gave little information about the pathological LN stages in the AIRT group. It is therefore not possible to ascertain whether these represented patients at a high risk (pN2/3 and/or ENE) or at a relatively low risk

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(pN1) for regional recurrence. The series of both Franks et al. [17] and Graafland et al. [13] used the same criteria for AIRT (two or more involved inguinal LNs and/or ENE). The differences in reported regional recurrence rates (43% at 3 yr vs 16.4% at 5 yr) are not explained but might be due to referral bias and delay. The risk of referral bias in the series by Graafland et al. [13] is likely to be lower.

Unfortunately, insufficient data are presented by Johnstone et al. [18] to give significant weight to any conclusions from the data, as the potential biases are all uncertain. However, it is highly likely that selection bias in that data set is high and problematic as the number of patients is very small for an international multicentre dataset. Despite this, they present the largest published data set in high-risk patients, those with ENE. This is the very cohort that the current iteration of the EAU guidelines suggest consideration be given to AIRT and for whom these data indicate that AIRT has no significant impact upon either recurrence or survival.

3.4.2. *Impact of review findings on clinical practice and further research*

Overall, it is clear that despite improvements in LN staging in penile cancer, survival of node-positive patients remains poor. The published literature to date does not provide evidence that inguinal AIRT in node-positive penile cancer patients after radical ILND has an impact on survival. Data on the associated toxicity of AIRT are almost completely lacking. As such, based on the available evidence, AIRT following ILND cannot be recommended in routine clinical practice.

The results of this review generate a number of possible hypotheses. Firstly, AIRT may be ineffective in significantly modifying the clinical outcome of patients with node-positive penile cancer simply given the propensity of the disease to spread systemically. However, the available data on regional recurrence suggest that AIRT may simply be ineffective, possibly due to differences in radiosensitivity of different SCC histological subtypes. Alternatively, AIRT may have a role that has yet to be identified from the limited retrospective data available. These questions will remain unanswered without prospective investigation of adjuvant therapy including AIRT.

4. Conclusions

Based upon the existing sparse evidence, there is no indication that AIRT following ILND offers any benefit to men with penile cancer and lesser still if any potential benefits of AIRT following ILND outweigh the risks of toxicity. Therefore, at present, until better evidence is available, inguinal AIRT in node-positive penile cancer patients after inguinal radical ILND is not recommended as part of standard clinical practice, and should be regarded as experimental and therefore restricted to prospective controlled clinical trial settings only.

Author contributions: Richard Robinson 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.

Study concept and design: Robinson, Watkin, Necchi.
Acquisition of data: Robinson, Coscione, MacPepple, Adewuyi, Yuan.
Analysis and interpretation of data: Robinson, Marconi.
Drafting of the manuscript: Robinson.
Critical revision of the manuscript for important intellectual content: Robinson, Marconi, Hakenberg, Watkin, Lam, MacLennan, Minhas, Compérat, Necchi.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.04.003.

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