Asian Journal of Urology 9 (2022) 389–406

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajur

Review

Updates in the use of radiotherapy in the management of primary and locally-advanced penile cancer

Akshar Patel [a], Arash O. Naghavi [b], Peter A. Johnstone [b], Philippe E. Spiess [c], G. Daniel Grass [b,*]

[a] *University of South Florida Morsani College of Medicine, Tampa, FL, USA*
[b] *Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA*
[c] *Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA*

Received 12 November 2021; received in revised form 20 February 2022; accepted 5 May 2022
Available online 9 September 2022

KEYWORDS
Brachytherapy;
Chemoradiation;
Radiation;
Radiotherapy;
Penile cancer;
Squamous cell carcinoma of the penis;
Penile-sparing;
Penile metastase;
Human papillomavirus

Abstract *Objective:* Penile cancer is a rare malignancy in most developed countries, but may represent a significant oncologic challenge in certain African, Asian, and South American regions. Various treatment approaches have been described in penile cancer, including radiotherapy. This review aimed to provide a synopsis of radiotherapy use in penile cancer management and the associated toxicities. In addition, we aimed to discuss palliative radiation for metastases to the penis and provide a brief overview of how tumor biology may assist with treatment decision-making.
Methods: Peer-reviewed manuscripts related to the treatment of penile cancer with radiotherapy were evaluated by a PubMed search (1960–2021) in order to assess its role in the definitive and adjuvant settings. Selected manuscripts were also evaluated for descriptions of radiation-related toxicity.
Results: Though surgical resection of the primary is an excellent option for tumor control, select patients may be treated with organ-sparing radiotherapy by either external beam radiation or brachytherapy. Data from randomized controlled trials comparing radiotherapy and surgery are lacking, and thus management is frequently determined by institutional practice patterns and available expertise. Similarly, this lack of clinical trial data leads to divergence in opinion regarding lymph node management. This is further complicated in that many cited studies evaluating lymph node radiotherapy used non-modern radiotherapy delivery techniques. Groin toxicity from either surgery or radiotherapy remains a challenging problem and further risk assessment is needed to guide intensification with multi-modal therapy.

* Corresponding author.
E-mail address: daniel.grass@moffitt.org (G.D. Grass).
Peer review under responsibility of Tongji University.

https://doi.org/10.1016/j.ajur.2022.05.010

Intrinsic differences in tumor biology, based on human papillomavirus infection, may help aid future prognostic and predictive models in patient risk stratification or treatment approach.
Conclusion: Penile cancer is a rare disease with limited clinical trial data driving the majority of treatment decisions. As a result, the goal of management is to effectively treat the disease while balancing the importance of quality of life through integrated multidisciplinary discussions. More international collaborations and interrogations of penile cancer biology are needed to better understand this disease and improve patient outcomes.

1. Introduction

Penile cancer mostly affects men past the age of 60 years old and has a prevalence between 0.1 and 1 per 100 000 men in developed countries; however, in certain Asian, African, and South American countries, this may comprise up to 10% of male malignancies [1]. Approximately 2000 new cases occur in the United States [2] and about 26 000 globally per year [3]. The variance in global incidence is related to multiple risk factors such as human papillomavirus (HPV) infection, tobacco exposure, chronic inflammation, and diverse circumcision practices [1]. Due to diversity in socioeconomic and cultural practices, penile squamous cell carcinoma (PSCC) incidence can vary substantially within a single region or country [4]. Most (95%) invasive penile cancers arise from mucosal cells of squamous origin and are termed PSCC. The most common site of tumor development is on the glans (35%—48%) [5,6] with approximately 40% being localized disease, which has a 5-year overall survival (OS) rate of approximately 90% [7]. Many patients with localized disease may be treated with therapeutic circumcision, partial or total penectomy with urethrostomy. When organ-sparing surgery is not feasible, a penectomy has been associated with a detriment in quality of life, which encompasses urinary and sexual function as well as mental health [8]. In patients with regional metastatic disease, the OS can range between 10% and 80% based on the burden of nodal disease despite aggressive inguinopelvic lymph node dissections, chemotherapy, and external beam radiotherapy (EBRT) [9].

Dating back to the early to mid-20th century, clinicians have debated on whether surgery, radiation therapy, or a combination of both should be used in the management of PSCC. An alternative definitive approach in select patients is penile-conserving radiotherapy, which may include EBRT or brachytherapy. These approaches may provide opportunity for organ preservation around 70%—90% and reserve surgery for salvage without a decrease in OS [10]. The role of EBRT in more locoregionally advanced disease is controversial as the supporting data are heterogenous and sometimes conflicting. Many of the unanswered questions in multi-modality management are being addressed in the ongoing International Advanced Penile Cancer Trial (InPACT) [11].

High quality evidence is lacking for the management of PSCC and current treatment is commonly based on institutional practice patterns and available expertise. At present, there are no validated biomarkers to guide treatment recommendations, though emerging data suggest HPV infection status may be predictive of radiation response in some patients.

2. Methods

An extensive literature review was conducted within PubMed for all peer-reviewed manuscripts written in the English language between 1960 and 2021 related to the management of penile cancer with radiotherapy. Key search words included "penile cancer", "penile squamous cell carcinoma", "penile metastasis", "radiotherapy", and "brachytherapy", independently and with Boolean queries. Given the limited number of articles on the topic, manual investigation of citations within identified articles was also performed. Clinicopathologic, treatment, outcome, and toxicity data were extracted from manuscripts where available for patients treated by radiotherapy with or without chemotherapy.

3. Radiotherapy as definitive management for primary penile cancer

The debate on whether to use radiotherapy, surgery, or both in PSCC management has been ongoing for more than 50 years [12,13]. At present, data from randomized controlled trials comparing radiotherapy and surgery are lacking, and thus management is frequently determined by institutional practice patterns and available expertise. This is reflected in a recent National Cancer Database analysis evaluating local management trends in the United States for locally invasive cT1-T3 PSCC where radiation was utilized in 2%—3% of cases between 2004 and 2013 [14]. Additional population-based studies noted less than 1% of patients with early stage disease are treated with radiotherapy [15] and less than 0.5% are treated with brachytherapy [16]. Thus, definitive EBRT or brachytherapy is chosen infrequently for the management of localized PSCC.

Due to psychosocial consequences associated with deformative penile surgery, organ-sparing surgery or a preservation approach with EBRT or brachytherapy in patients with suitable tumor characteristics is advised; this view is supported by the European Association of Urology (EAU) guidelines [17]. Though local recurrence rates with organ-sparing surgery range between 5% and 30%, cancer-specific survival (CSS) may not differ in early stage

tumors following a local recurrence, but may be worse in patients with more aggressive disease presentations [18,19]. Radiation has been used in patients who wish to avoid penectomy or are elderly and frail. The approach with definitive radiation depends on the size, location, and invasive characteristics of the tumor. Commonly selected tumor attributes suitable for preservation with radiation are superficial or exophytic lesions measuring less than 4 cm in size and localized to the glans or coronal sulcus. Although, tumors less than 4 cm and on the glans with less than 1 cm of invasion may also be suitable for definitive radiation.

3.1. External beam radiation

Localized PSCC may be treated with various penile-sparing techniques, topical therapy (*e.g.* 5-fluorouracil and imiquimod) [20], or penile-sparing surgeries [21]. EBRT may also provide the opportunity for functional preservation and adequate tumor control. A major advantage of EBRT is its wide availability and ease of implementation by a radiation oncologist, though a disadvantage is the protracted time required to achieve the desired tumor response over the course of treatment. There are several small heterogeneous cohort series described in the literature, which span a range of tumor staging systems and radiation approaches, reflecting the evolution of treatment approaches over the last several decades. Overall, an approach with EBRT may provide penile preservation rates between 36% and 66% at 5-year (Table 1).

A series from Princess Margaret Hospital demonstrated patients with Tis/T1a ($n=11$) achieved complete responses with no recurrences at a median follow-up of 7 years; this study used a variety of dose and fractionation schedules making conclusions on treatment approach difficult to interpret [22]. As most superficial cases are treated with non-radiation approaches, more advanced disease presentation usually necessitates treating the full thickness of the penis. This requires positioning the penis in a manner to maintain daily reproducibility of target coverage while sparing surrounding normal tissues. A suitable method is to encase the penis in a tissue-equivalent block with a central cylinder. At present, it is recommended to use conventional fractionation to a total dose of 66—70 Gy with fraction sizes of at least 2 Gy. From the selected case series, dosing regimens range from 25 Gy to 74 Gy over a variable number of fractions [22—27] and poor tumor response has been associated with total dose less than 60 Gy [25,28,29]. More hypofractionated approaches with 50—55 Gy in 16 fractions may be associated with worse long-term toxicity [24,26]. Classically, EBRT yields a local control rate of 60% (range: 41%—69%) with 5-year cause-specific survival of 60% [22,24—27].

3.1.1. Treatment set-up

In preparing a patient for definitive EBRT, a radical circumcision is recommended upfront to reduce risk of paraphimosis, foreskin contracture, or tissue necrosis. It is also important to address sperm preservation when necessary. Very localized and superficial lesions (*e.g.*, Tis, T1a) may be treated by orthovoltage (125 kilovoltage) or 9 MeV electrons with bolus and lead cut outs, similar to skin cancer set-ups. The electron energy should be chosen to ensure that the 90% isodose line achieves coverage at depth with 100% coverage at the surface. For more advanced disease, a block with tissue-equivalent electron density can house the penis and hold it in position to ensure coverage of the entire length and surface when needed. EBRT can be delivered with parallel opposed lateral fields using 4—6 MV energy. Care should be taken to shield the groin and testes with a lead block when needed.

In more advanced disease, radiation to the primary and nodal regions may warranted, but there should be consideration of concurrent chemotherapy. We refer readers to an excellent review on EBRT set-up for more details on positioning and target delineation [30].

3.2. Brachytherapy

Brachytherapy is also a suitable alternative to penectomy in patients with localized PSCC, though this approach is not as widely available due to the need for specific expertise. Patient selection for brachytherapy ideally includes disease limited to the glans, less than 4 cm in diameter, and less than 1 cm of invasion [31—33]. With doses ranging from 38 Gy to 70 Gy, the use of brachytherapy offers 5-year local control and penile preservation rates ranging approximately from 70% to 90%, with 5-year OS rates of 63%—100% [10,34], which are comparable to surgical series [35]. The 5-year local control rates vary between T1 (89%—91%), T2 (75%—78%), and T3 (50%—71%) stage of disease [33,36]. Crook et al. [28] also demonstrated no differences in local control with brachytherapy between well-differentiated and moderate/poorly-differentiated tumor histology, though more aggressive disease raises the risk of nodal metastases. Early series reported brachytherapy is associated with a higher penile preservation rate than EBRT (78% *vs.* 64%) [37]. In a meta-analysis by Hasan et al. [35], brachytherapy offered superior local control and penile preservation when compared to EBRT (5-year: 50% and 49%, respectively), which translated to a significantly higher OS. In this analysis, brachytherapy offered a similar 5-year local control to penectomy (79% *vs.* 84%) without a significant difference in OS (73% *vs.* 76%). This suggests that even in those with a local recurrence after brachytherapy, surgical salvage with penectomy could be employed without an impact on OS.

All forms of brachytherapy offer similar disease control and toxicity (Table 2). Earlier studies predominantly utilized low dose rate (LDR) brachytherapy, with 50—70 Gy delivered continuously over 5 days with a classic dose rate of 50—60 cGy per hour [28,31—33,36,38—43]. The use of high dose iridium-192 given in hourly pulses (50—60 cGy per pulse), or pulse dose rate brachytherapy, is treated with similar dosimetric parameters, but between pulses, offers less radiation exposure risk to healthcare staff and family [42,43]. More common employment of high dose rate (HDR) brachytherapy offers a similar local control/penile preservation rate, but utilizing a hypofractionated regimen with comparable bioequivalent dosing with 30—54 Gy over 5—9 days using a twice daily (BID) regimen [10,44—49]. Recently, HDR has come into favor due to patient

Table 1 Use of EBRT in definitive management of primary penile squamous cell carcinoma.

Study	Pts, *n*	RT dose, Gy	Median follow-up, month	5-year LC, %	5-year CSS, %	5-year penile preservation, %	Stenosis or necrosis rate	Tumor characteristic	Tumor location
McLean et al., 1993 [22]	26	35 Gy/10 fx; 60 Gy/25 fx	116	61	69	66	• NR (seven Pts with late complications)	• 73.1% T1; 15.3% T2; 7.7% T3; 3.9% T4	• 65% glans or prepuce; 4% shaft; 31% multiple sites
Sarin et al., 1997 [29]	59	60 Gy/30 fx	62	55	66	50	• 3% necrosis; 14% stenosis	• 86.4% T1; 8.5% T2; 1.7% T3; 3.4% T4	• In 101 Pts, 78% were confined to glans; only 59 received EBRT
Gotsadze et al., 2000 [25]	155	40—60 Gy	40	65	86	65	• 1% necrosis; 7% stenosis	• 36.8% T1; 55.5% T2; 7.7% T3;	• NR
Zouhair et al., 2001 [27]	23	45—74 Gy/25—37 fx	12	41	NR	36	• 10% stenosis	• 29% T1; 59% T2; 10% T3; 2% Tx	• In 41 Pts: 41% glans; 22% prepuce; 20% shaft; 10% corona; 5% prepuce or glans; 2% prepuce or shaft
Azrif et al., 2006 [24]	41	50.0—52.5 Gy/16 fx	41	62	96	62	• 8% necrosis; 29% stenosis	• 90.2% T1; 9.8% T2	• 98% glans/prepuce
Ozsahin et al., 2006 [23]	21	52 Gy	62	49	NR	52	• 10% stenosis	• 37% T1; 53% T2; 8% T3; 2% Tx	• In 60 Pts: 40% glans; 26% prepuce; 22% shaft; 7% corona; 3% prepuce/glans; 1% prepuce/shaft
Mistry et al., 2007 [26]	18	55 Gy/16 fx—50 Gy/20fx	62	63	NR	62	• 10% necrosis; 5% stenosis	• 23.5% Tx; 17.6% *in situ*; 35.3% T1; 17.6% T2; 6% T3	• In 65 Pts: 76% were on glans/prepuce; 5% on shaft

CSS, cancer-specific survival; EBRT, external beam radiotherapy; Pts, patients; RT, radiotherapy; LC, local control; NR, not reported.

Table 2 Use of brachytherapy in management of primary penile squamous cell carcinoma.

Study	Brachytherapy type	Patient, *n*	RT dose, median (range), Gy	Follow-up, median (range), month	5-year LC, %	5-year CSS, %	5- year penile preservation, %	Stenosis or necrosis rate	Tumor characteristic
Crook et al., 2005 [38]	Pulsed dose rate	49	60 (NR)	33.4 (4.0–140.0)	85.3	90	86.5	• 16% necrosis; 12% stenosis	• 51% T1; 33% T2; 8% T3; 4% Tx; 4% *in situ*
Crook et al., 2009 [28]	Pulsed dose rate/low dose rate	67	60	48.0 (2.4–194.4)	87.3	83.6	88.0	• 16% necrosis; 12% stenosis	• 56% T1; 33% T2; 8% T3; 3% Tx
de Crevoisier et al., 2009 [41]	Low dose rate	144	65 (37–75)	68.4 (6.0–348.0)	80.0 (at 10 years)	92.0 (at 10 years)	7.0 (at 10 years)	• 26% necrosis; 29% stenosis	• Confined to glans, N0
Pimenta et al., 2015 [42]	Low dose rate	25	60 (50–65)	110.4 (0.0–228.0)	NR	91.3 (at 5 years and 10 years)	86.1	• 0% necrosis; 43% stenosis	• T1-T2
Cordoba et al., 2016 [40]	Low dose rate	73	60 (40–70)	51.0 (33.4–68.7)	NR	91.4	87.6	• 6.8% necrosis; 6.6% stenosis	• 91.8% of lesions on glans • 75.3% T1 lesions; 15% T2; 1.3% Tx
Kellas-Sleczka et al., 2019 [44]	High dose rate	76	28–54.8[a] (median EQD2); 47.4–55.1[b] (median EQD2)	76.0 (7.0–204.0)	65.6	85.0	69.5	• 2.6% necrosis; 1.3% stenosis	• 11.8% *in situ*; 46.1% T1; 21.1% T2; 9.2% T3; 11.8% Tx
Martz et al., 2021 [10]	High dose rate	29	36 (31–39)	72.4 (3–174)	82.0	88.0	79.3	• 10.3% necrosis; 17% telangiectasia	• T1-T2, N0–N2, M0

CSS, cancer-specific survival; RT, radiotherapy; LC, local control, NR, not reported; EQD2, equivalent dose in 2 Gy fractions.

[a] Superficial high-dose-rate.

[b] Interstitial high-dose-rate.

convenience, less patient isolation due to lower risk of radiation exposure to staff, and adjustable source dwell time allowing for dose optimization of the target and normal tissue.

Brachytherapy can either be delivered with interstitial therapy, surface mold, or a hybrid of the two. Interstitial LDR/pulse dose rate requires catheter spacing 12—18 mm between adjacent needles, whereas HDR requires 10—12 mm spacing to avoid hot-spots during dosimetry optimization. Surface mold or "plesiotherapy" can be utilized to treat tumors up to 5 mm in depth or can be used in conjunction with interstitial catheters to improve surface dose and dosing homogeneity (Fig. 1). Additional technical details on penile brachytherapy can be found in the American Brachytherapy Society (ABS) and Groupe Européen de Curiethérapie/European Society for Therapeutic Radiation and Oncology (GEC-ESTRO) guidelines [50] as well the experience from Crook et al. [51] with their high-volume experience. Common toxicities with brachytherapy include acute radiodermatitis with a late presentation of soft tissue necrosis (0%—26%) and urethral stenosis (1%—45%) [32,33,36,37,39,41]. With the use of dose optimization in HDR, an approach of 3 Gy BID fractionation to 42—54 Gy has been shown to provide local control and penile preservation rates of 86%—100%, with no necrosis or stenosis by limiting the volume receiving 125% and 150% of the prescription dose (*i.e.*, V125 and V150, respectively) [47,49]. The ABS-GEC ESTRO guidelines for penile brachytherapy recommends V125 of less than 50%, V150 of less than 25%, limiting confluent areas of 125% to skin surface, as well as limiting urethral dosing to V115 of less than 10% and V90 of less than 95% [50]. Rouscoff et al. [45] utilized HDR to 36—39 Gy in nine fractions with a 5-year local control of 92% and a stenosis and necrosis of 8%, by limiting the V150 of less than 25%, V200 of less than 10 mm, and avoiding confluent V200 isodose lines. Thus, with modern day treatment planning and utilization of HDR, previously seen toxicities can be minimized. Fig. 1 demonstrates an example of HDR penile brachytherapy performed at our institution, which employed the volumetric constraints mentioned previously to minimize toxicity.

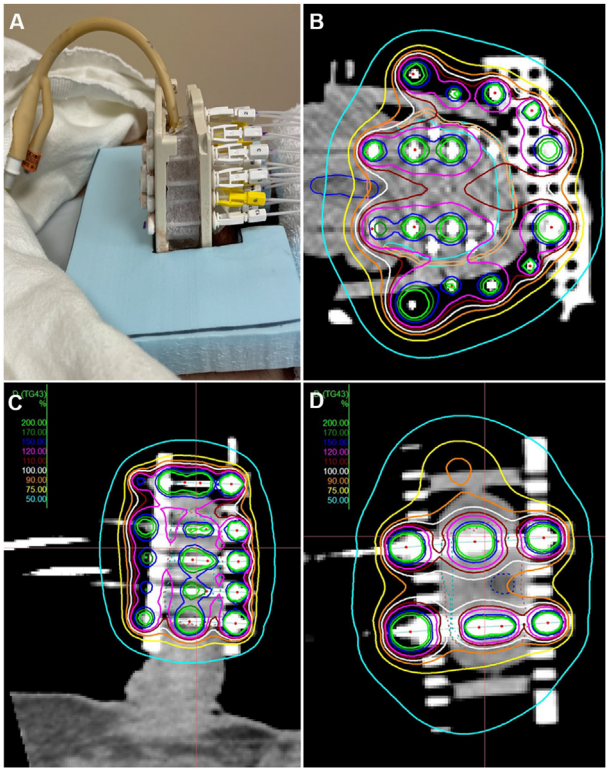

Figure 1 High dose rate interstitial penile brachytherapy. (A) Example of a mobile hybrid implantation with interstitial catheters, bolus with external catheters to supplement superficial dose and aid in homogeneity, along with a foley in place during the duration of the implant; (B—D) Treatment planning of a bilateral glans tumor. (B) Axial; (C) Sagittal; (D) Coronal. Note the catheter spacing and dosing, limiting the V150 (blue) and V200 (green) volume to mitigate stenosis/necrosis risk. Note the catheter spacing from the urethra/meatus and supplementing dose from outside of the bolus, allowing a homogenous plan and limiting urethral toxicity. Note the supplemental dose from outside the template contributing to the target volume.

4. Adjuvant radiotherapy

4.1. Management of primary site

Commonly, adjuvant treatment to the primary site and nodal basins can be considered separately based on risk factors. The role of post-operative EBRT to the primary site is not clearly defined in the literature. Langsenlehner et al. [52] reported a 28.5% 5-year local recurrence rate in a subset of patients ($n=14$) following incomplete surgical resection who were treated with post-operative EBRT with 45—50 Gy with a boost to the surgical stump up to 60 Gy. Similarly, Zouhair et al. [27] reported a local relapse rate of 25% in patients with positive surgical margins treated with post-operative EBRT. Though the data are limited, post-operative EBRT in patients with positive margins may improve local control and prevent additional tumor-related morbidity.

4.2. Management of nodal sites

PSCC has a high propensity for spread to the inguinal lymph nodes (ILNs) and pelvic lymph nodes (PLNs), which is the most important prognostic factor for survival. PSCC follows a step-wise nodal echelon spread pattern with the most advanced regional disease culminating in the PLNs. Accordingly, survival substantially decreases with nodal burden and location [53], with PLN metastases having a 5-year OS less than 30% [54]. A comprehensive description of the surgical management of lymph nodes is beyond the scope of this review; thus we refer readers to an excellent review on this topic by Leone et al. [55].

There are several important points to highlight for the treating radiation oncologist since surgical management of lymph nodes is important to consider when formulating EBRT nodal target volumes in either the definitive or adjuvant setting. First, the optimal management for patients with clinically node negative (cN0) disease is currently undefined and continues to evolve with "risk-adapted" staging

approaches characterized by sentinel lymph node mapping or modified superficial lymphadenectomy [56]. Even with a modified superficial inguinal lymphadenectomy, morbidity rates can be as high as 30%–40% [57].

If there are palpable or radiologically-evident inguinal nodes (clinically-positive [cN+]) or histologic confirmation on intra-operative assessment (pathologically-positive [pN+]), then a bilateral radical inguinal lymphadenectomy is often indicated. However, if these nodes are fixed or bulky, then neoadjuvant chemotherapy is commonly recommended followed by consolidative surgery [55]. PLN dissection is usually advised if there is evidence of ≥2 ILNs, extranodal extension (ENE), or obvious pelvic nodal disease [17,58]. Patients with positive ILN have an estimated pelvic node risk of 20%–65% [59]. Due to the lack of nodal cross-over, bilateral PLN dissection is only considered if increased risk factors are appreciated in the bilateral ILNs or there is evidence of bilateral PLNs' involvement; it should be noted that subjecting a patient to a PLN dissection is controversial as 5-year OS is less than 10% and risk of morbidity is substantial [60].

4.2.1. Management of cN0 inguinal node

The role of prophylactic groin EBRT in cN0 patients is unclear. The ILN occult metastasis rate in patients with aggressive primary tumor features (*e.g.*, >T2, poor differentiation, and perineural invasion) can be about 20%–30% [61]. Data from the 1950s have demonstrated that elective groin EBRT using 30–40 Gy results in approximately a 5% risk of pathologic ILN metastases [12,62]; these findings led some to believe groin EBRT cannot eradicate micrometastatic disease as this is a similar percentage seen with surgical evaluation in cN0 patients [63]. Due to these data, a watch-and-wait approach has been advocated for patients with cN0, yet the EAU and National Comprehensive Cancer Network (NCCN) guidelines are conflicting on recommendations. The EAU guidelines only recommend groin radiation for palliation [17], whereas the NCCN guidelines suggest to consider prophylactic EBRT to ILNs in non-surgical candidates or those who decline surgery [64]. Some providers advised against elective EBRT to the groins because there are few gained benefits and the risk of radiation-related toxicity is high; this is a similar philosophy to early ILN dissection.

The study cited by the EAU guidelines to support no benefit to prophylactic groin EBRT is from Kulkarni and Kamat [65], which compared bilateral ILN dissection, bilateral ILN EBRT, or surveillance in 37 cN0 and 27 cN1-2a (palpable inguinal nodes, but not metastatic) patients within a prospective non-randomized trial from 1979 to 1982. Eighteen of these patients were treated with EBRT, in which 12 (67%) were cN0 and 6 (33%) were cN1-2a. Although this study identified increased 5-year OS in the surgical versus EBRT group (74% *vs.* 66%), relapse occurred in only two patients (2/18; 11%) with EBRT [65]. In this study, EBRT was delivered to the inguino-femoral region using 50 Gy over a 5–6 week period, though no additional details of radiation fields and energies are described. Given the years of this study, it can be assumed two-dimensional (2D) planning was employed, possibly with cobalt-60, using opposed fields treated to midplane with or without supplemental electron fields to boost the groins.

The Gynecologic Oncology Group 88 trial evaluated ILN dissection versus prophylactic groin EBRT (50 Gy in 25 fractions prescribed to 3 cm depth in the groin) following resection of the primary cN0 vulvar cancer. This study was stopped early due to excessive groin recurrences in the EBRT arm, suggesting a lack of benefit for groin EBRT in cN0 patients [66]. This EBRT approach in the Gynecologic Oncology Group 88 is similar to earlier PSCC studies, but Koh et al. [67] demonstrated that prescribing to this depth (3 cm) using computed tomography-based planning leads to inferior inguinal nodal coverage, as the median patient depth was approximately 6.0 cm (range: 2.0–18.5 cm); this results in EBRT doses of less than 50 Gy, which may not be sufficient in patients with high-risk primary disease and occult ILN metastasis rates of about 20%–30%.

4.2.2. Management of ILN cN+ or pN+

In patients with cN+ or pN+ ILNs, inguinal EBRT may provide improved locoregional control, though adjuvant inguinal lymph node EBRT (AIRT) has not been vigorously evaluated. For this reason, there currently is no level I evidence to define the role of AIRT in PSCC. The NCCN guidelines (version 2.2021) recommend adjuvant EBRT if any of the following high-risk features are present: positive surgical margins, ≥2 pelvic nodal metastases, ENE, bilateral inguinal nodal involvement, or ≥4 cm tumor deposit in lymph nodes [64]. Interestingly, Winters et al. [68] found that patients treated at academic centers were 50% less likely to receive AIRT compared to those treated at community cancer programs, which suggests academic physicians may prefer not to treat patients without level I evidence compared to non-academic practices. It should be noted that this is in contrast to the EAU guidelines, which indicate adjuvant EBRT should not be given due to the lack of prospective data [17]. Select studies evaluating adjuvant ILN with or without PLN radiation and chemotherapy ± PLN ± chemotherapy are shown in Table 3.

Earlier studies, using antiquated EBRT delivery techniques (*e.g.*, no megavoltage energies, thus beam penetration to target region is of question) have demonstrated less than optimal tumor control in the groins [12,69,70] and have supported the view that EBRT to the groins does not provide substantial benefit [71]. A study by Mistry et al. [26] describes 65 patients treated between 1993 and 2003, in which eight underwent ILN dissection with one treated with AIRT; the surgery alone group had a groin recurrence rate of 43% (3/7) versus 0% (0/1) with AIRT. In this study, four patients with cN+ disease received EBRT alone with palliative intent using doses ranging from 12 Gy to 40 Gy in a hypofractionated manner, which resulted in 50% groin control rate [26]. It is hard to draw conclusions from this study about ILN EBRT efficacy.

A systematic review by Robinson et al. [72] identified only seven studies suitable for evaluating AIRT following lymph node dissection, all of which were retrospective, highly heterogeneous, and limited by high selection bias. As this analysis is the most robust to date, it is important to highlight several aspects of the cohorts that form the basis of the authors conclusions, which recommend against AIRT. First, this analysis encompassed 1605 patients, of which only 114 had data available for AIRT-specific evaluation. The regional recurrence rate following AIRT ranged from 10% to 92%

(derived from five studies). Three of the studies were from patients treated from the 1950s to late 1990s, and thus the majority of these patients were treated with 2D treatment planning. This is an important point as conventional EBRT fields were based on bony landmarks, and as subsequent studies in vulvar cancer have demonstrated, this 2D approach leads to inferior target coverage in the deep-seated inguinal-femoral nodal regions [67], though this has not been formally evaluated in the adjuvant setting for PSCC.

The largest cohort in the study by Djajadiningrat et al. [7] ($n=944$, 1956–2012) provided no information on the number of men receiving AIRT nor the ILN recurrence rates following EBRT. They indicated that AIRT was given to patients with $\geq$2 ILN positive and/or ENE on pathology evaluation, which was delivered with 50 Gy/25 fractions. This dataset overlaps with the study by Graafland et al. [73], which described a cohort of 161 patients, of which 67 were treated with ipsilateral AIRT for similar indications as the former study using non-volumetric planning. The overall 5-year ILN recurrence rate was 16%, but the recurrence rates in all the patients treated with AIRT are not provided. It is noted that of the 26 patients that had an inguinal recurrence, 42% received AIRT and three of these relapsed during treatment [73].

The 2nd largest cohort ($n=285$) by Ravi et al. [74] contains a subset of only 12 patients treated with adjuvant groin EBRT due to ENE, in which the 5-year disease-free survival (DFS) was 8% in those 12 patients. The AIRT in this study was delivered with 2D planning and dose to the groins was not defined. Interestingly, this study found that pre-operative groin EBRT for patients ($n=38$) with mobile nodes $\geq$4 cm reduced the rate of ENE to 8% and resulted in only 3% of patients having a post-operative groin recurrence [74]. The study by Demkow [75] described a series of 64 men, of which about half underwent ILN dissection. The 12 patients that received AIRT had a 17% OS rate at a median follow-up of 33 months. No details on the radiation approach were provided [74].

Chen and Wu [76] reported a subset of 40 men with PSCC, of whom 14 underwent ILN dissection, and of these, nine received AIRT. The radiation included high energy 10–15 MV photons or a mixed field with 12 MeV electrons to boost the inguinal fields. The depth was prescribed to the deepest margin of the femoral vessels with CT-based planning, or 4–5 cm if non-volumetric planning was utilized. The median radiation dose was 54 Gy (range: 40–70 Gy) using conventional fractionation, which was described to cover the primary site, areas of local extension, bilateral ILNs, and lower iliac lymph nodes. With this approach, only one (11%) patient had a regional recurrence with AIRT compared to 60% (3 of 5) of patients with ILN dissection alone. Franks et al. [77] described a series of 23 men, in which 14 were treated with adjuvant radiation to both the ILNs and PLNs between 2002 and 2008. All of these patients who underwent CT-based volumetric planning with coverage of the bilateral iliac, inguinal, obturator, and presacral nodes were treated with 45 Gy in 20 fractions with or without an additional 12 Gy boost to areas at risk. Six patients (43%) had locoregional recurrence at 3 years and ENE portended worse tumor control [77]. These data form the basis of the EAU guidelines, which currently do not recommend AIRT.

An important point to consider when critically evaluating these data is the radiation approaches used in these studies. Mittal et al. [78] recently analyzed the location of greater than 200 ILNs in 33 patients with cN+ PSCC and found that 99% of nodes were anterior (81% antero-medial and 18% antero-lateral) to the femoral vessels with 95% being superior to the pubic symphysis; with these data they proposed variable margin expansions off the vessels to encompass at least 95% of mapped ILNs. The implementation of intensity-modulated radiation therapy with daily image guidance now provides the opportunity for three-dimensional CT-based anatomic delineation coupled with highly conformal dose coverage, which can reduce dose to skin, bowel, bladder, femoral heads, and genitalia in order to reduce toxicity [79]. With increasing use of implementation of intensity-modulated radiation therapy in the management of PSCC, it is prudent to reevaluate the efficacy of ILN EBRT.

4.2.3. Management of pN3 inguinal nodes with ENE or pelvic nodes with or without ENE

In patients with pN3 disease, adjuvant chemotherapy is commonly recommended as it has been demonstrated to improve OS after surgery. This is supported by a pooled retrospective analysis suggesting adjuvant chemotherapy may be superior for patients with pN3 following inguino-pelvic lymph node dissection, though these patients were younger, had less aggressive histology and less bilateral inguinal disease [80]. Other studies (all with less than 20 patients) have also suggested adjuvant chemotherapy can improve tumor control [81]. More recently, neoadjuvant chemotherapy is being used in patients with positive PLNs, which is supported by data extrapolated from patients with unresectable, bulky, or fixed inguinal nodes. These data suggested about 50% response rates resulting in one-third of patients being alive at least 2 years after therapy [82,83].

Whether EBRT provides a benefit in this subset of patients is a topic of debate, as data are mixed and from heterogeneous small cohorts treated with various chemotherapy and radiation sequences. Tang et al. [84] described a multi-institutional cohort of 40 pN3 (pelvic node) patients treated with adjuvant pelvic radiation; and at a median follow-up of 9.3 months, they identified improved disease-specific survival (14.4 *vs.* 8 months) and time to recurrence (7.7 *vs.* 5.3 months) with adjuvant pelvic radiation versus no radiation. A population-based analysis found that at a median follow-up of 25 months, concurrent chemoradiation (CRT) did not improve CSS in comparison to chemotherapy in all-comers, but was superior to chemotherapy alone in the pN3 subset ($n = 77$) with a 2-year CSS of 51% versus 24% [84]. The data by Johnstone et al. [85] included a pooled multi-institutional cohort of 93 patients with pN3 disease and despite adjuvant EBRT (50 Gy in 25 fractions), 81% of ENE sites had a recurrence in the treatment field. Interestingly, risk of recurrence was independent of ENE or whether adjuvant EBRT was administered, which may be related to an elevated baseline risk in this poor prognostic population. Yuan et al. [86] reported on 34 patients (88% received concurrent chemotherapy) treated with adjuvant radiation for pN2 and pN3 with a median dose of 50 Gy (range:

Table 3 Select studies evaluating adjuvant EBRT ± chemotherapy to the groin or pelvis.

Study	Treatment years	Patient, *n*	LND, *n*	EBRT, *n*	Age, median (IQR), year	Median follow-up, month	Chemotherapy, *n* or %	Adjuvant EBRT target
Demkow, 1999 [75]	1989–1994	64	35	12	64 (21–86)	33.0	NACT: 2; CCRT: 3	NR
Zouhair et al., 2001 [27]	1962–1994	41	5	14	59 (35–75)	70.0	No	ILN
Chen et al., 2004 [108]	1989–2000	45	19	9	64 (29–87)	37.0	CT: 1	Primary/bilateral ILN and lower iliac LN
Langsenlehner et al., 2008 [52]	1987–2006	24	8	Penis/surgical stump (n=14); ILN (n=8)	62.7 (35.5–90.4)	58.4	No	Penis/stump/ILN & iliac nodes
Franks et al., 2011 [77]	2002–2008	23	14	14	58 (40–81)	27.0	No	Bilateral ILN and PLN
Graafland et al., 2011 [73]	1988–2007	161	161	67	64 (33–91)	60.0	NACT: 4	Ipsilateral ILN ± PLN
Tang et al., 2017 [84]	1980–2013	92	92	40	65.3 (53–70)	9.3	Perioperative CT: 27	Bilateral PLN
Winters et al., 2018 [68]	1998–2012	589	589	136	61.8 (NR)	NR	Perioperative CT: 169	ILN + PLN
Johnstone et al., 2019 [85]	Multi-institutional (NR)	93	93	58	65.3 (36–90)	9.4	Perioperative CT: 46	ILN ± PLN (ipsilateral if involved)
Ager et al., 2021 [87]	2002–2017	146	146	121	59 (54–70)	10.6	CCRT: 41%	Ipsilateral ILN ± pelvic LN
Choo et al., 2020 [89]	1995–2015	23	23	11	57 (43–68)	15.8	CCRT: 11	Bilateral ILN & PLN
Li et al., 2021 [91]	2003–2015	93	93	32	49 (NR)	8.8	CCRT: 34%	NR
Jaipuria et al., 2020 [90]	2011–2017	45	45	31	56 (45–67)	12.5	CCRT: 6	Bilateral ILN and PLN + suprapubic region
Yuan et al., 2020 [123]	1999–2016	51	47	19	61 (37–91)	36.6	CCRT: 17; CT alone: 20	PLN (n=15); ILN (n=13)
Mittal et al., 2021 [78]	2014–2017	14	14	14	NR	24.0	CT: 14	Bilateral ILN ± PLN
Khurud et al., 2022 [88]	2010–2018	128	128	78	57 (50–65)	22.0	CT alone: 19%; CCRT: 13%; CT into EBRT: 24%; CT into CCRT: 12%	Variable: involved ILN and PLN (68%); involved & uninvolved ILN + PLN (32%)

(continued on next page)

Table 3 (*continued*)

Study	EBRT indication	EBRT technique	EBRT dose to LN	5-yr CSS	5-yr OS	5-yr LRC	EBRT-related toxicity	Misc data
Demkow, 1999 [75]	≥2 ILNs or ENE	NR	NR	NR	NR (3-yr: 76%)	NR	NR	LR: 11% (entire cohort)
Zouhair et al. , 2001 [27]	(+) surgical margins or lymph node involvement	Parallel opposed AP/PA fields (18 MV); e-field boost for positive nodes	36—66 Gy/20—36 fx	NR	57%	48%	NR	pN2: 7%; pN3: 1%
Chen et al. , 2004 [108]	pN+	Parallel opposed AP/PA field	40—70 Gy/20—35 fx	NR	54.30%	NR (3-yr: 89% [AIRT group])	Grade 3 lymphedema: 22% (AIRT); radionecrosis of inguinal region: 11% (AIRT group)	pN+ (*n*=17)
Langsenlehner et al., 2008 [52]	(+) surgical margins and pN+	Parallel opposed AP/PA fields; e-field boost for positive nodes	45—60 Gy/25—60 fx	84.30%	56.60%	100% with AIRT	10% with persistent lymphedema	Of 12 patients with cN+, definitive EBRT to ILN resulted in 5-yr regional control of 92%
Franks et al., 2011 [77]	pN2/3 or ENE	Parallel opposed AP/PA fields; e-field boost for positive nodes	Phase I: 45 Gy/20 fx; Phase II: 12 Gy/5 fx (boost if needed)	NR	NR (3-yr: 66%)	NR (3-yr: 56%)	Scrotal/penile/lower leg lymphedema: 6	Locoregional relapse-free survival: 56%
Graafland et al., 2011 [73]	≥2 ILNs or ENE	NR	50 Gy/25 fx	NR	NR	NR	NR	5-yr ILN recurrence: 16%
Tang et al., 2017 [84]	pN3	NR	50 Gy/25 fx (*n*=27); <40 Gy (*n*=4); >50 Gy (*n*=5)	14.4 months	12.2 months	Adjuvant EBRT with better median time to recurrence (7.7 *vs.* 5.3 months)	NR	Median PLN+ (*n*=2); ENE+ in PLN (*n*=39)
Winters et al., 2018 [68]	NR	NR	75% received ≥ 45 Gy	NR	64%	NR	NR	pN2 (*n*=433)
Johnstone et al., 2019 [85]	≥2 ILNs or ENE	NR	50 Gy in 25 fx	NR	Median OS: 10.6 months	NR	NR	Median ILN+ (*n*=4), 72% ENE; median PLN+ (*n*=2), 49% ENE; median DSS: 11 months
Ager et al., 2021 [87]	pN3	NR	Variable: 45 Gy/20 fx; 54 Gy/27 fx; 50—54 Gy/25—27 fx	51%	44%	56%	NR	ENE: 99% (ILN: 74%; PLN: 25%); 5-yr RFS: 51%; in-field recurrence: 47%

(*continued on next page*)

Table 3 (*continued*)

Study	EBRT indication	EBRT technique	EBRT dose to LN	5-yr CSS	5-yr OS	5-yr LRC	EBRT-related toxicity	Misc data
Choo et al., 2020 [89]	Regional LN+	NR	45 Gy/25 fx (uninvolved LN); 56 Gy/28 fx (involved LN)	NR (2-yr: 49.3%)	NR (2-yr: 25%)	NR (2-yr: 27%)	Lymphedema: 46%; necrosis: 9%	pN3: 43%
Li et al., 2021 [91]	pN3	Parallel opposed AP/PA fields (equally weighted)	30–68 Gy/15–34 fx	NR (3-yr CSS: 28.5% [CCRT] *vs.* 16.2% [CT])	NR	NR	NR	21% CCRT underwent salvage surgery
Jaipuria et al., 2020 [90]	≥2 ILNs ± PLN ± ENE	IMRT/VMAT	45 Gy/25 fx (pelvis); 54 Gy (ENE+ region); 57–60 Gy (gross residual)	NR	Mean OS: 3.9 yr (RT); mean OS: 2.8 yr (Chemo); median OS not met in PLN-cohort	NR	39% of RT group with persistent lymphedema; no RT-related necrosis	Pelvic LN+ (n=13); ENE: 78%
Yuan et al., 2020 [123]	NR	NR	39.6–54 Gy/22–30 fx (PLN); 42.5–64.8 Gy (ILN)	NR	NR	2-yr: 54%	G2 skin: 18% (acute); G2 GI; 12% (acute); G1 lymphedema: 18% (late)	N2/3 (n=23); ENE+: 12%
Mittal et al., 2021 [78]	pN3	IMRT	50 Gy/25 fx	NR	NR (2-yr: 79%)	NR (2-yr: 79%)	G2 lymphedema: 29%; G3 lymphedema: 0%	93% received adjuvant and CCRT
Khurud et al., 2022 [88]	pN3	Conventional (54%); 3DCRT (26%); IMRT (20%);	45 Gy/25 fx; 50.4 Gy/28 fx; 50 Gy/25 fx	NR	NR (2-yr: 62%)	NR (2-yr: 83% [multi-modal])	45% of AIRT group with lymphedema	2-yr DFS: 55%

EBRT, external beam radiotherapy; NR, not reported; IMRT, intensity-modulated radiation therapy; CSS, cancer-specific survival; OS, overall survival; Misc, miscellaneous; ILN, inguinal lymph nodes; ENE, extranodal extension; PLN, pelvic lymph node; NACT, neoadjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; LND, lymph node dissection; LN, lymph node; LRC, local regional control; AP, anterior posterior; PA, posterior anterior; DSS, disease specific survival; DFS, disease free survival; RFS, relapse free survival; VMAT, volumetric modulated arc therapy; RT, radiotherapy; DCRT, definitive chemoradiotherapy; yr, year; Chemo, chemotherapy; AIRT, adjuvant inguinal lymph node EBRT; IQR, interquartile range; fx, fractions.

42.5—64.8 Gy), which provided 60% locoregional control at a follow-up of 12 months.

Ager et al. [87] reported on 121 patients with ENE (74% inguinal and 25% pelvic) treated between 2002 and 2017 at two hospitals that underwent ILN dissection with or without dissection of PLN, followed by a complete course of adjuvant EBRT (41% received concurrent chemotherapy) and found a 5-year relapse free survival of 51%, CSS of 51%, and OS of 44%. The EBRT doses in this study varied from 45 Gy in 20 fractions or 50—60 Gy in 25—30 fractions; in-field recurrence was two-fold higher in patients receiving 50 Gy or less. Khurud et al. [88] recently reported a retrospective study of 128 men with pN3 (24% with pelvic nodes with 57% having ENE) treated with adjuvant chemotherapy ($n=24$; 19%), radiation alone ($n=16$; 12%) or multimodality therapy (48%) characterized by CRT ($n=16$; 13%), sequential chemotherapy and radiation ($n=31$; 24%), or chemotherapy and CRT ($n=15$; 12%). Overall, about 50% of patients had a regional relapse, in which 19% recurred following RT (20% were in-field), though patients treated with intensified sequential chemotherapy and CRT adjuvant therapy had improved DFS. This study found chemotherapy and radiation have similar DFS and OS in only ILN positive patients, but sequential chemotherapy and CRT were superior in PLN+ patients.

Choo et al. [89] evaluated 11 patients at Mayo Clinic who underwent inguinopelvic lymph node dissection (72% with pN3) and found a 2-year CSS of 55% with adjuvant CRT versus surveillance (28%); it should be noted the CRT group had a higher proportion of patients with pN3, greater than five lymph nodes, and ENE compared to the surveillance group. The EBRT target volumes in this study included the bilateral ILNs and PLNs with an average dose of 56 Gy in 28 fractions to involved regions and 45 Gy to uninvolved nodes, which resulted in 55% risk of locoregional relapse. Another case series reported by Jaipuria et al. [90] found that adjuvant EBRT in ILN+ only patients provided better OS compared to chemotherapy, though in patients with PLN+ disease, CRT provided no benefit over chemotherapy.

Last, a modern pooled study of 93 patients with pN3 (ENE) in the ILNs demonstrated superior 3-year CSS (29% *vs.* 16%) with adjuvant CRT versus adjuvant chemotherapy alone [91]. Pond et al. [92] reported poor outcomes with CRT in locally-advanced PSCC ($n=21$) with a median OS of 10 months. Though the authors mention the median EBRT dose was 49 Gy, there is no separate description of the dose used in non-metastatic patients, which may be the reason why EBRT dose was associated with improved OS and progression-free survival for every 10 Gy increase [92]. Overall, pN3 has variable outcomes with PLN positivity being associated with worse outcomes. Adjuvant CRT is expected to provide roughly 50% CSS at 2—5 years based on these data.

Overall, there is still uncertainty surrounding the effectiveness of adjuvant inguinal or pelvic EBRT in patients with node positive cancer due to the lack of randomized control trials. The majority of evidence is limited by small patient numbers, heterogenous treatment approaches as well as indications for treatment selection. Typically, radiotherapy should be avoided in patients that are cN0, as radiotherapy related complications outweigh the few benefits that patients may receive from treatment [55]. Though prospective data have demonstrated that other anogenital squamous malignancies (*e.g.*, anus, cervical, and vulvar) have improved outcomes with CRT [30], the burden of supporting evidence in PSCC is scarce. The world eagerly awaits the results of the InPACT to resolve some of these questions, which also provide guidance on target delineation for radiation planning [11]. In this regard, Fig. 2 is an example of a patient treated with adjuvant CRT targeting the prepubic fat, bilateral ILN, and PLN basins.

5. Management of penile cancer metastases to the penis

Metastatic cancer to the penis is very rare with no consensus on the optimal treatment approach. The first case was described in the late 1800s by Eberth with about 500 cases described since then [93,94], with most being in the setting of metachronous spread [95]. A review of the literature by Hizli and Berkmen [96] found the most common primary tumors metastasizing to the penis are the bladder (34.7%), prostate (29.8%), rectum-sigmoid colon (15.7%), and kidney (6.5%). Despite the infrequency, penile metastases should be addressed, even in the presence of multi-site metastases, as these patients may become symptomatic with swelling, ulceration, and severe pain. With advancements in imaging approaches [97], occult metastases may be identified without symptoms [98,99].

Malignant priapism, or painful induration and erection of the penis secondary to tumor invasion, may occur in 20%—40% of men, which requires palliative treatment [100]. There are a handful of case series describing the efficacy of palliative radiotherapy for penile metastases with a recent review identifying 42 cases of malignant priapism originating from various primary origins; in this review, only 38% of cases were addressed with radiotherapy [100]. A range of radiation doses have been described utilizing standard palliative approaches (*e.g.*, 8 Gy in one fraction, 20—30 Gy in 5—10 fractions) or more aggressive approaches up to 60 Gy in 30 fractions [100,101]; notably, some patients achieved pain relief with lower doses, whereas other achieved minimal response with higher doses. Given the dearth of data to guide metastases to the penis, a multidisciplinary discussion should guide treatment recommendations with the overall goal of care directed at palliation to improve quality of life.

6. Radiation-related toxicities

Management of penile cancer with radiotherapy is associated with certain toxicities and potential risk for long-term complications. Complication risks differ whether the target is the intact penis or nodal basins and by the form and total dose of radiation utilized. The degree of skin toxicity may vary by intrinsic patient sensitivity, body habitus, dose per fraction, bolus administration, or use of chemotherapy.

Acutely, EBRT delivered with conventional fractionation (*e.g.*, 2 Gy per fraction) may result in mild penile edema, radiodermatitis, and moist desquamation. Most acute skin reactions were resolved in 2—4 weeks, but chronic skin changes such as telangiectasias, hyperpigmentation, and

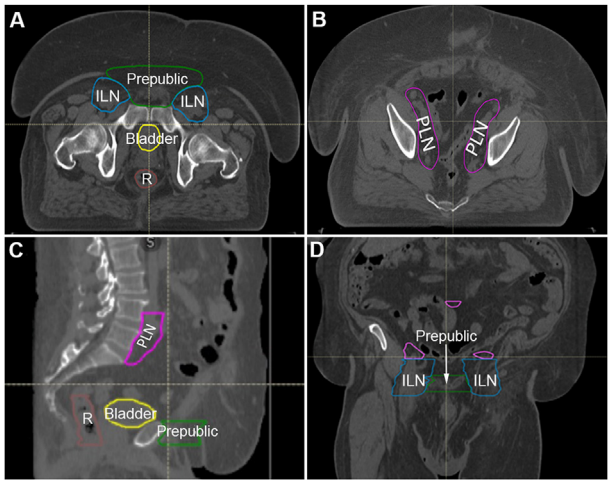

Figure 2 Adjuvant EBRT to prepubic fat and bilateral ILNs and PLNs. Case of a 55-year-old male with hrHPV− pT3 N3 M0 poorly differentiated PSCC of the glans status post partial penectomy with mons panniculectomy requiring reconstruction with split thickness graft. Approximately 2 months later he underwent bilateral superficial and deep ILN dissection with pathology demonstrating negative margins at the primary site and 3/15 ILNs involved with malignancy with evidence of bilateral ENE. (A and B) Axial slices showing the prepubic space (green), bilateral ILNs (blue), and bilateral PLNs (pink) clinical target volumes; (C) Sagittal view demonstrating prepubic space and PLN coverage; (D) Coronal view showing prepubic space and ILN interface. Other organs at risk include bladder (yellow) and rectum (brown). The patient was treated with 52 Gy to the prepubic fat and bilateral PLNs and 62.4 Gy to the bilateral ILNs over 26 fractions with concurrent weekly cisplatin. EBRT, external beam radiotherapy; ILN, lymph node; PLN, pelvic lymph node; hrHPV, high-risk HPV; PSCC, penile squamous cell carcinoma; ENE, extranodal extension; R, rectum.

superficial scarring may present at later follow-up. Use of conventional fractionation may result in a skin necrosis risk of 1%—3%, whereas hypofractionated approaches can increase this risk to 8%—10% [34]. Conservative measures to maintain skin barrier protection and maximize hygiene are necessary to minimize these toxicities.

The penis is susceptible to develop necrosis from brachytherapy with the risk varying based on LDR versus HDR approaches, depth of tumor invasion, and dose distribution required for target coverage. LDR experiences have reported necrosis risk at 0%—26% with HDR having a risk of 0%—8%. The acute moist desquamation may present 2—3 weeks after brachytherapy and can take upwards of 2—3 months to resolve. If necrosis develops, it usually occurs within the first 1—2 years [30]. As stated previously, close attention to patient selection and volume-dose constraints provided by the ABS-GEC ESTRO guidelines [50] may reduce these risks compared to historical experiences. Following local tumor control, necrosis is the most common reason for loss of organ preservation, which is supported by the experience of Rozan et al. [37] where about 30% of men underwent penile amputation secondary to treatment related necrosis. Hyperbaric oxygen may be an effective treatment option for severe and refractory tissue necrosis [102].

A dreaded complication seen after radiation, either EBRT or brachytherapy, is meatal stenosis. Stenosis can cause major detriment to urinary and sexual quality of life. Similar to necrosis, the risk of stenosis can increase from 10% to 30% with the use of hypofractionated EBRT. Some LDR and HDR experiences have reported stenosis rates up to 45% and from 0% to 40%, respectively [10,34]. This risk may vary based on interstitial versus surface mold approaches or proximity of needles to distal tip of glans [34]. If stenosis develops acutely, it is usually treated with early iterative dilatation to minimize risk for chronic stricture formation. In one series, 9% of patients required penectomy secondary to severe fibrosis, but this remains relatively uncommon [42].

With penile preservation, maintenance of sexual function is important for many men [103]. A small study done by Delaunay et al. [104] found that approximately 60% of sexually active men maintained sexual activity after brachytherapy with 95% also maintaining erections. At a median follow-up of 5.9 years, Gambachidze et al. [105] reported 70% of men maintained sexual activity with little erectile dysfunction in a questionnaire study. Martz et al. [10] also reported no significant detriment in sexual function using the International Index of Erectile Dysfunction-5 score. Thus, there may be a high chance for maintenance of sexual function following definitive therapy to an intact penis.

Additionally, patients who have undergone total or partial penectomy resulting in perineal urethrostomy (PU) may require adjuvant radiation therapy for high-risk features. de Vries et al. [106] recently reported on a 20-year multi-institutional cohort of 299 patients undergoing PU and found a crude rate of 12% for developing stenosis, of which 74% required surgical revision within 1 year. Data on the use of radiation in the setting of a PU are limited. Within this same patient cohort, Johnstone [107] reported rates of PU stenosis in the subset that received adjuvant EBRT ($n=37$) were not significantly different compared to those not treated with EBRT (19% *vs.* 11%); the adjuvant EBRT group had a lower frequency of surgical revision (5% *vs.* 9%), which may be due to exclusion of the PU in the EBRT field unless positive surgical margins are appreciated.

The toxicity following AIRT or pelvic RT is not well defined. Modern series of ILN dissection suggested surgical complication risks (*e.g.*, wound infection, dehiscence, necrosis, and lymphedema) may range between 40% and 60%, but vary widely based on approach [55]. In series that reported lymphedema rates, AIRT is associated with a risk between 22% and 45% [78,88—90,100,108].

The risk of secondary malignancy following radiation is also of concern, especially in younger men, but overall this risk remains extremely low. Ravi [109] described a cohort of five patients who were treated with EBRT (>50 Gy) for PSCC and later developed a secondary poorly-differentiated carcinoma at a mean of 13 years. Similarly, two cases have been described following interstitial brachytherapy

after 15 years and a single case of angiosarcoma was reported at 18 years [110]. Therefore, long-term surveillance in young men is warranted following radiotherapy to the penis.

7. Radiation in the era of molecular biology

Infection with high-risk HPV (hrHPV) has been associated with approximately 30%—50% of PSCC cases, but may vary depending on population studied and method of detection [111—113]. Data regarding the prognostic impact of hrHPV infection are mixed. An earlier study by Bezerra et al. [114] examined 82 cases and detected hrHPV DNA in 31% of PSCC tumors, but after adjusting for clinicopathologic factors no difference in 10-year OS was noted based on hrHPV infection status. Similarly, in a study of grouped primary and metastatic PSCC patients ($n=29$), hrHPV infection status was also not prognostic of survival [115]. In contrast, Lont et al. [116] described a series of 171 men (29% hrHPV+) and found differences in 5-year DFS favoring HPV positivity (92% *vs.* 78%). In a separate and updated analysis within the overlapping Dutch cohort, hrHPV+ remained associated with improved 5-year DFS (96% *vs.* 82%) even after adjusting for other variables [117]. Though there are contradictory findings across institutional cohorts, a recent systematic review and meta-analysis of 20 studies found both hrHPV- and p16-positivity were associated with improved tumor control compared to HPV- or p16-negative patients [118].

There are little data on how HPV status influences responsiveness to EBRT in PSCC. This was first explored by Yuan et al. [119] in a study of 51 men (45% hrHPV+), which found that in men treated with adjuvant CRT ($n=17$), HPV+ provided an absolute 45% improvement in 2-year locoregional control compared to HPV− men. Similarly, a multi-institutional study by Bandini et al. [120] found that peri-operative EBRT in 49 patients (82% adjuvant) resulted in improved median OS in the HPV+ versus HPV− patients, which remained significant in propensity core matching up to 10 years of follow-up. Thus, it is possible that the molecular machinery of HPV+ tumors is distinct from HPV− tumors and that this may influence radiation sensitivity. A hypothesis-generating study using the genomic-adjusted radiation dose [121], which is derived from the radiosensitivity index, a 10-gene signature that estimates intrinsic radiation sensitivity [122], suggested 50% of PSCC patients treated with 50—54 Gy would achieve adequate locoregional control [86,123]. These data suggested uniform radiation dosing has not yet been optimized based on underlying patient tumor biology.

HPV-driven PSCC tumors have distinct genomic profiles and mutational frequencies compared to their HPV− counterparts [124,125]. A common finding in profiling HPV-mediated tumors is the lack of *TP53* mutations, which has been seen PSCC [120]. The p53 biology is complex and context dependent, and thus p53 staining via immunohistochemistry may not fully recapitulate the complexity of p53-mediated radiation responses, which appear to be driven by dynamic signaling events in a tissue-dependent manner [126]. Therefore, HPV status should be evaluated in future investigations describing the effects of RT or CRT in regard to PSCC response [127]. Given the broad molecular orchestration guided by HPV genomes and p53, future studies are likely to identify novel biomarkers to help guide treatment decisions in this population.

8. Conclusion

Penile cancer is a rare disease with limited clinical trial data driving the majority of treatment decisions. As a result, the goal of management for the tumor should be to effectively treat the disease while balancing the importance of quality of life. Radiation therapy is underutilized and radiation oncologists should be proactive in educating surgical and dermatology colleagues of the utility of radiation as a functional penile-sparing modality. In specific instances, radiotherapy can be used in the adjuvant management of the primary and nodal sites post resection; however, there is lack of quality evidence demonstrating the effectiveness of radiotherapy in these cases. The data gathered from the InPACT will further help develop better management options for these patients. As the molecular revolution continues to advance, additional insights will be gained when comparing tumors by HPV infection status. At present, preliminary data suggest HPV+ tumors may be more radiosensitive, but this requires further validation.

Author contributions

Study concept and design: Akshar Patel, Arash O. Naghavi, G. Daniel Grass.
Data acquisition: Akshar Patel, Arash O. Naghavi, G. Daniel Grass.
Data analysis: Akshar Patel, Arash O. Naghavi, G. Daniel Grass.
Drafting of manuscript: Akshar Patel, Arash O. Naghavi, Peter A. Johnstone, Philippe E. Spiess, G. Daniel Grass.
Critical revision of the manuscript: Peter A. Johnstone, Philippe E. Spiess, G. Daniel Grass.

Conflicts of interest

Philippe E. Spiess is the President of Global Society of Rare Genitourinary Tumors, the vice-chair NCCN bladder and penile cancer, and a member of ASCO/EAU penile cancer panel. Other authors declare no other conflict of interest.

References

[1] Douglawi A, Masterson TA. Penile cancer epidemiology and risk factors: a contemporary review. Curr Opin Urol 2019;29:145—9.
[2] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7—33.
[3] Montes Cardona CE, Garcia-Perdomo HA. Incidence of penile cancer worldwide: systematic review and meta-analysis. Rev Panam Salud Publica 2017;41:e117. https://doi.org/10.26633/RPSP.2017.117.
[4] Vieira CB, Feitoza L, Pinho J, Teixeira-Júnior A, Lages J, Calixto J, et al. Profile of patients with penile cancer in the region with the highest worldwide incidence. Sci Rep 2020;10:2965. https://doi.org/10.1038/s41598-020-59831-5.

[5] Barnholtz-Sloan JS, Maldonado JL, Pow-sang J, Giuliano AR. Incidence trends in primary malignant penile cancer. Urol Oncol 2007;25:361—7.

[6] Hernandez BY, Barnholtz-Sloan J, German RR, Giuliano A, Goodman MT, King JB, et al. Burden of invasive squamous cell carcinoma of the penis in the United States, 1998-2003. Cancer 2008;113:2883—91.

[7] Djajadiningrat RS, Graafland NM, van Werkhoven E, Meinhardt W, Bex A, van der Poel HG, et al. Contemporary management of regional nodes in penile cancer—improvement of survival? J Urol 2014;191:68—73.

[8] Maddineni SB, Lau MM, Sangar VK. Identifying the needs of penile cancer sufferers: a systematic review of the quality of life, psychosexual and psychosocial literature in penile cancer. BMC Urol 2009;9:8. https://doi.org/10.1186/1471-2490-9-8.

[9] Pagliaro LC, Crook J. Multimodality therapy in penile cancer: when and which treatments? World J Urol 2009;27:221—5.

[10] Martz N, Bodokh Y, Gautier M, Thamphya B, Schiappa R, Lam Cham Kee D, et al. High-dose rate brachytherapy in localized penile cancer: 5-Year clinical outcome analysis. Clin Transl Radiat Oncol 2021;27:89—95.

[11] Canter DJ, Nicholson S, Watkin N, Hall E, Pettaway C; InPACT Executive Committee. The international penile advanced cancer trial (InPACT): rationale and current status. Eur Urol Focus 2019;5:706—9.

[12] Murrell DS, Williams JL. Radiotherapy in the treatment of carcinoma of the penis. Br J Urol 1965;37:211—22.

[13] Alexander LL, Medina A, Benninghoff DL, Camiel MR. Cancer of the penis. Radiation therapy or surgery. J Natl Med Assoc 1972;64:533—6.

[14] Menon H, Patel RR, Ludmir EB, Muralidhar V, Cushman TR, Amini A, et al. Local management of preinvasive and clinical T1-3 penile cancer: utilization of diverse treatment modalities. Future Oncol 2020;16:955—60.

[15] Shen X, Parker W, Miller L, TenNapel M. Opportunities for use of radiation therapy in penile cancer based on patterns of care in the United States from 2007 to 2013. Ther Adv Urol 2019;11:1756287219828972. https://doi.org/10.1177/1756287219828972.

[16] Mulherkar R, Hasan S, Wegner RE, Verma V, Glaser SM, Kalash R, et al. National patterns of care for early-stage penile cancers in the United States: how is radiation and brachytherapy utilized? Brachytherapy 2019;18:503—9.

[17] Hakenberg OW, Comperat EM, Minhas S, Necchi A, Protzel C, Watkin N. EAU guidelines on penile cancer: 2014 update. Eur Urol 2015;67:142—50.

[18] Kamel MH, Bissada N, Warford R, Farias J, Davis R. Organ sparing surgery for penile cancer: a systematic review. J Urol 2017;198:770—9.

[19] Roussel E, Peeters E, Vanthoor J, Bozzini G, Muneer A, Ayres B, et al. Predictors of local recurrence and its impact on survival after glansectomy for penile cancer: time to challenge the dogma? BJU Int 2021;127:606—13.

[20] Neubert T, Lehmann P. Bowen's disease—a review of newer treatment options. Ther Clin Risk Manag 2008;4:1085—95.

[21] Baumgarten A, Chipollini J, Yan S, Ottenhof SR, Tang DH, Draeger D, et al. Penile sparing surgery for penile cancer: a multicenter international retrospective cohort. J Urol 2018;199:1233—7.

[22] McLean M, Akl AM, Warde P, Bissett R, Panzarella T, Gospodarowicz M. The results of primary radiation therapy in the management of squamous cell carcinoma of the penis. Int J Radiat Oncol Biol Phys 1993;25:623—8.

[23] Ozsahin M, Jichlinski P, Weber DC, Azria D, Zimmermann M, Guillou L, et al. Treatment of penile carcinoma: to cut or not to cut? Int J Radiat Oncol Biol Phys 2006;66:674—9.

[24] Azrif M, Logue JP, Swindell R, Cowan RA, Wylie JP, Livsey JE. External-beam radiotherapy in T1-2 N0 penile carcinoma. Clin Oncol 2006;18:320—5.

[25] Gotsadze D, Matveev B, Zak B, Mamaladze V. Is conservative organ-sparing treatment of penile carcinoma justified? Eur Urol 2000;38:306—12.

[26] Mistry T, Jones RW, Dannatt E, Prasad KK, Stockdale AD. A 10-year retrospective audit of penile cancer management in the UK. BJU Int 2007;100:1277—81.

[27] Zouhair A, Coucke PA, Jeanneret W, Douglas P, Do HP, Jichlinski P, et al. Radiation therapy alone or combined surgery and radiation therapy in squamous-cell carcinoma of the penis? Eur J Cancer 2001;37:198—203.

[28] Crook J, Ma C, Grimard L. Radiation therapy in the management of the primary penile tumor: an update. World J Urol 2009;27:189—96.

[29] Sarin R, Norman AR, Steel GG, Horwich A. Treatment results and prognostic factors in 101 men treated for squamous carcinoma of the penis. Int J Radiat Oncol Biol Phys 1997;38:713—22.

[30] Korzeniowski MA, Crook JM. Contemporary role of radiotherapy in the management of penile cancer. Transl Androl Urol 2017;6:855—67.

[31] Soria JC, Fizazi K, Piron D, Kramar A, Gerbaulet A, Haie-Meder C, et al. Squamous cell carcinoma of the penis: multivariate analysis of prognostic factors and natural history in monocentric study with a conservative policy. Ann Oncol 1997;8:1089—98.

[32] Kiltie AE, Elwell C, Close HJ, Ash DV. Iridium-192 implantation for node-negative carcinoma of the penis: the Cookridge Hospital experience. Clin Oncol 2000;12:25—31.

[33] Mazeron JJ, Langlois D, Lobo PA, Huart JA, Calitchi E, Lusinchi A, et al. Interstitial radiation therapy for carcinoma of the penis using iridium 192 wires: the Henri Mondor experience (1970—1979). Int J Radiat Oncol Biol Phys 1984;10:1891—5.

[34] Crook J. Organ preserving radiation strategies for penile cancer. Urol Oncol 2022;40:184—90.

[35] Hasan S, Francis A, Hagenauer A, Hirsh A, Kaminsky D, Traughber B, et al. The role of brachytherapy in organ preservation for penile cancer: a meta-analysis and review of the literature. Brachytherapy 2015;14:517—24.

[36] Delannes M, Malavaud B, Douchez J, Bonnet J, Daly NJ. Iridium-192 interstitial therapy for squamous cell carcinoma of the penis. Int J Radiat Oncol Biol Phys 1992;24:479—83.

[37] Rozan R, Albuisson E, Giraud B, Donnarieix D, Delannes M, Pigneux J, et al. Interstitial brachytherapy for penile carcinoma: a multicentric survey (259 patients). Radiother Oncol 1995;36:83—93.

[38] Crook JM, Jezioranski J, Grimard L, Esche B, Pond G. Penile brachytherapy: results for 49 patients. Int J Radiat Oncol Biol Phys 2005;62:460—7.

[39] Chaudhary AJ, Ghosh S, Bhalavat RL, Kulkarni JN, Sequeira BV. Interstitial brachytherapy in carcinoma of the penis. Strahlenther Onkol 1999;175:17—20.

[40] Cordoba A, Escande A, Lopez S, Mortier L, Mirabel X, Coche-Déqueant B, et al. Low-dose brachytherapy for early stage penile cancer: a 20-year single-institution study (73 patients). Radiat Oncol 2016;11:96. https://doi.org/10.1186/s13014-016-0676-9.

[41] de Crevoisier R, Slimane K, Sanfilippo N, Bossi A, Albano M, Dumas I, et al. Long-term results of brachytherapy for carcinoma of the penis confined to the glans (N— or NX). Int J Radiat Oncol Biol Phys 2009;74:1150—6.

[42] Pimenta A, Gutierrez C, Mosquera D, Pera J, Martínez E, Londres B, et al. Penile brachytherapy—retrospective review of a single institution. Brachytherapy 2015;14:525—30.

[43] Escande A, Haie-Meder C, Mazeron R, Maroun P, Cavalcanti A, de Crevoisier R, et al. Brachytherapy for conservative treatment of invasive penile carcinoma: prognostic factors and long-term analysis of outcome. Int J Radiat Oncol Biol Phys 2017;99:563—70.
[44] Kellas-Sleczka S, Bialas B, Fijalkowski M, Wojcieszek P, Szlag M, Cholewka A, et al. Nineteen-year single-center experience in 76 patients with penile cancer treated with high-dose-rate brachytherapy. Brachytherapy 2019;18:493—502.
[45] Rouscoff Y, Falk AT, Durand M, Gal J, Chand ME, Gautier M, et al. High-dose rate brachytherapy in localized penile cancer: short-term clinical outcome analysis. Radiat Oncol 2014;9:142. https://doi.org/10.1186/1748-717X-9-142.
[46] Marban M, Crook J, Keyes M, Dubash R, Batchelar D. High-dose-rate brachytherapy for localized penile cancer: evolution of a technique. Brachytherapy 2020;19:201—9.
[47] Sharma DN, Joshi NP, Gandhi AK, Haresh KP, Gupta S, Julka PK, et al. High-dose-rate interstitial brachytherapy for T1-T2-stage penile carcinoma: short-term results. Brachytherapy 2014;13:481—7.
[48] Pohankova D, Sirak I, Kasaova L, Grepl J, Paluska P, Louda M, et al. High-dose rate brachytherapy in the treatment of early stages of penile carcinoma. Klin Onkol 2019;32:52—7.
[49] Petera J, Sirak I, Kasaova L, Macingova Z, Paluska P, Zouhar M, et al. High-dose rate brachytherapy in the treatment of penile carcinoma—first experience. Brachytherapy 2011;10:136—40.
[50] Crook JM, Haie-Meder C, Demanes DJ, Mazeron JJ, Martinez AA, Rivard MJ. American Brachytherapy Society-Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement for penile brachytherapy. Brachytherapy 2013;12:191—8.
[51] Crook J, Jezioranski J, Cygler JE. Penile brachytherapy: technical aspects and postimplant issues. Brachytherapy 2010;9:151—8.
[52] Langsenlehner T, Mayer R, Quehenberger F, Prettenhofer U, Langsenlehner U, Pummer K, et al. The role of radiation therapy after incomplete resection of penile cancer. Strahlenther Onkol 2008;184:359—63.
[53] Ficarra V, Akduman B, Bouchot O, Palou J, Tobias-Machado M. Prognostic factors in penile cancer. Urology 2010;76:S66—73. https://doi.org/10.1016/j.urology.2010.04.008.
[54] Pandey D, Mahajan V, Kannan RR. Prognostic factors in node-positive carcinoma of the penis. J Surg Oncol 2006;93:133—8.
[55] Leone A, Diorio GJ, Pettaway C, Master V, Spiess PE. Contemporary management of patients with penile cancer and lymph node metastasis. Nat Rev Urol 2017;14:335—47.
[56] Thomas A, Necchi A, Muneer A, Tobias-Machado M, Tran ATH, Van Rompuy AS, et al. Penile cancer. Nat Rev Dis Prim 2021;7:11. https://doi.org/10.1038/s41572-021-00246-5.
[57] Coblentz TR, Theodorescu D. Morbidity of modified prophylactic inguinal lymphadenectomy for squamous cell carcinoma of the penis. J Urol 2002;168:1386—9.
[58] Clark PE, Spiess PE, Agarwal N, Biagioli MC, Eisenberger MA, Greenberg RE, et al. Penile cancer: clinical practice guidelines in oncology. J Natl Compr Canc Netw 2013;11:594—615.
[59] Protzel C, Alcaraz A, Horenblas S, Pizzocaro G, Zlotta A, Hakenberg OW. Lymphadenectomy in the surgical management of penile cancer. Eur Urol 2009;55:1075—88.
[60] Zargar-Shoshtari K, Djajadiningrat R, Sharma P, Catanzaro M, Zhu Y, Nicolai N, et al. Establishing criteria for bilateral pelvic lymph node dissection in the management of penile cancer: lessons learned from an international multicenter collaboration. J Urol 2015;194:696—701.
[61] Slaton JW, Morgenstern N, Levy DA, Santos MW, Tamboli P, Ro JY, et al. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal lymph node metastasis in penile squamous cancer. J Urol 2001;165:1138—42.
[62] Ekstrom T, Edsmyr F. Cancer of the penis; a clinical study of 229 cases. Acta Chir Scand 1958;115:25—45.
[63] Heyns CF, Fleshner N, Sangar V, Schlenker B, Yuvaraja TB, van Poppel H. Management of the lymph nodes in penile cancer. Urology 2010;76:S43—57.
[64] Network NCC. Penile cancer (version 2.2021). Available from: URL: https://www.nccn.org/professionals/physician_gls/pdf/penile.pdf.
[65] Kulkarni JN, Kamat MR. Prophylactic bilateral groin node dissection versus prophylactic radiotherapy and surveillance in patients with N0 and N1-2A carcinoma of the penis. Eur Urol 1994;26:123—8.
[66] Stehman FB, Bundy BN, Thomas G, Varia M, Okagaki T, Roberts J, et al. Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys 1992;24:389—96.
[67] Koh WJ, Chiu M, Stelzer KJ, Greer BE, Mastras D, Comsia N, et al. Femoral vessel depth and the implications for groin node radiation. Int J Radiat Oncol Biol Phys 1993;27:969—74.
[68] Winters BR, Kearns JT, Holt SK, Mossanen M, Lin DW, Wright JL. Is there a benefit to adjuvant radiation in stage III penile cancer after lymph node dissection? Findings from the National Cancer Database. Urol Oncol 2018;36:e11—6. https://doi.org/10.1016/j.urolonc.2017.11.005.
[69] Bouchot O, Auvigne J, Peuvrel P, Glemain P, Buzelin JM. Management of regional lymph nodes in carcinoma of the penis. Eur Urol 1989;16:410—5.
[70] el-Demiry MI, Oliver RT, Hope-Stone HF, Blandy JP. Reappraisal of the role of radiotherapy and surgery in the management of carcinoma of the penis. Br J Urol 1984;56:724—8.
[71] Horenblas S. Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: the role and technique of lymph node dissection. BJU Int 2001;88:473—83.
[72] Robinson R, Marconi L, MacPepple E, Hakenberg OW, Watkin N, Yuan Y, et al. 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. Eur Urol 2018;74:76—83.
[73] Graafland NM, Moonen LM, van Boven HH, van Werkhoven E, Kerst JM, Horenblas S. Inguinal recurrence following therapeutic lymphadenectomy for node positive penile carcinoma: outcome and implications for management. J Urol 2011;185:888—93.
[74] Ravi R, Chaturvedi HK, Sastry DV. Role of radiation therapy in the treatment of carcinoma of the penis. Br J Urol 1994;74:646—51.
[75] Demkow T. The treatment of penile carcinoma: experience in 64 cases. Int Urol Nephrol 1999;31:525—31.
[76] Chen WK, Wu ZG. Adding radiotherapy based on chemotherapy can improve cancer-specific survival in N3 penile cancer: a SEER-based study. Transl Androl Urol 2020;9:2587—95.
[77] Franks KN, Kancherla K, Sethugavalar B, Whelan P, Eardley I, Kiltie AE. Radiotherapy for node positive penile cancer: experience of the Leeds teaching hospitals. J Urol 2011;186:524—9.
[78] Mittal R, Krishnatry R, Maitre P, Murthy V. Recommendations and clinical validation of inguinal clinical target volume delineation in penile cancer. Int J Radiat Oncol Biol Phys 2021;111:741—53.
[79] Milano MT, Jani AB, Farrey KJ, Rash C, Heimann R, Chmura SJ. Intensity-modulated radiation therapy (IMRT) in

the treatment of anal cancer: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 2005;63:354–61.
[80] Sharma P, Djajadiningrat R, Zargar-Shoshtari K, Catanzaro M, Zhu Y, Nicolai N, et al. Adjuvant chemotherapy is associated with improved overall survival in pelvic node-positive penile cancer after lymph node dissection: a multi-institutional study. Urol Oncol 2015;33:e417–23. https://doi.org/10.1016/j.urolonc.2015.05.008.
[81] Peyraud F, Allenet C, Gross-Goupil M, Domblides C, Lefort F, Daste A, et al. Current management and future perspectives of penile cancer: an updated review. Cancer Treat Rev 2020;90:102087. https://doi.org/10.1016/j.ctrv.2020.102087.
[82] Bermejo C, Busby JE, Spiess PE, Heller L, Pagliaro LC, Pettaway CA. Neoadjuvant chemotherapy followed by aggressive surgical consolidation for metastatic penile squamous cell carcinoma. J Urol 2007;177:1335–8.
[83] Leijte JA, Kerst JM, Bais E, Antonini N, Horenblas S. Neoadjuvant chemotherapy in advanced penile carcinoma. Eur Urol 2007;52:488–94.
[84] Tang DH, Djajadiningrat R, Diorio G, Chipollini J, Ma Z, Schaible BJ, et al. Adjuvant pelvic radiation is associated with improved survival and decreased disease recurrence in pelvic node-positive penile cancer after lymph node dissection: a multi-institutional study. Urol Oncol 2017;35:e617–23. https://doi.org/10.1016/j.urolonc.2017.06.001.
[85] Johnstone PAS, Boulware D, Djajadiningrat R, Ottenhof S, Necchi A, Catanzaro M, et al. Primary penile cancer: the role of adjuvant radiation therapy in the management of extranodal extension in lymph nodes. Eur Urol Focus 2019;5:737–41.
[86] Yuan Z, Grass GD, Azizi M, Ahmed KA, Yoder GSJ, Welsh EA, et al. Intrinsic radiosensitivity, genomic-based radiation dose and patterns of failure of penile cancer in response to adjuvant radiation therapy. Rep Pract Oncol Radiother 2019;24:593–9.
[87] Ager M, Njoku K, Serra M, Robinson A, Pickering L, Afshar M, et al. Long-term multicentre experience of adjuvant radiotherapy for pN3 squamous cell carcinoma of the penis. BJU Int 2021;128:451–9.
[88] Khurud P, Krishnatry R, Telkhade T, Patil A, Prakash G, Joshi A, et al. Impact of adjuvant treatment in pN3 penile cancer. Clin Oncol (R Coll Radiol) 2022;34:172–8.
[89] Choo R, Nehra A, Zattoni F, Pagliaro LC, Karnes RJ. Is there any benefit in adding postoperative adjuvant concurrent radiotherapy and chemotherapy for penile cancer with regional lymph node metastasis? Minerva Urol Nefrol 2020;72:474–81.
[90] Jaipuria J, Kohli T, Venkatasubramaniyan M, Singh A, Gupta S, Pathak P, et al. Adjuvant radiation compares favorably to chemotherapy in patients with carcinoma penis and nodal positivity restricted to groin. Urol Oncol 2020;38:641.e9–18. https://doi.org/10.1016/j.urolonc.2020.03.026.
[91] Li ZS, Li XY, Wang B, Chen P, Li X, Augusto OA, et al. Radiotherapy plus chemotherapy versus chemotherapy alone in penile cancer patients with extracapsular nodal extension after inguinal lymph node surgery: a multi-institutional study. World J Urol 2021;39:113–9.
[92] Pond GR, Milowsky MI, Kolinsky MP, Eigl BJ, Necchi A, Harshman LC, et al. Concurrent chemoradiotherapy for men with locally advanced penile squamous cell carcinoma. Clin Genitourin Cancer 2014;12:440–6.
[93] De Luca F, Zacharakis E, Shabbir M, Maurizi A, Manzi E, Zanghì A, et al. Malignant priapism due to penile metastases: case series and literature review. Arch Ital Urol Andro 2016;88:150–2.
[94] Marcu D, Iorga L, Mischianu D, Bacalbasa N, Balescu I, Bratu O. Malignant priapism—what do we know about it? In Vivo 2020;34:2225–32.
[95] Cherian J, Rajan S, Thwaini A, Elmasry Y, Shah T, Puri R. Secondary penile tumours revisited. Int Semin Surg Oncol 2006;3:33. https://doi.org/10.1186/1477-7800-3-33.
[96] Hizli F, Berkmen F. Penile metastasis from other malignancies. A study of ten cases and review of the literature. Urol Int 2006;76:118–21.
[97] Davidson T, Domachevsky L, Giladi Y, et al. Penile secondary lesions: a rare entity detected by PET/CT. Sci Rep 2021;11:5912. https://doi.org/10.1038/s41598-021-85300-8.
[98] Spinapolice EG, Fuccio C, Rubino B, Palumbo R, Mensi M, Scopesi L, et al. Penile metastases from bladder and prostate cancer detected by PET/CT: a report of 3 cases and a review of literature. Clin Genitourin Cancer 2014;12:e155–9. https://doi.org/10.1016/j.clgc.2014.03.013.
[99] Parida GK, Tripathy S, Roy SG, Singhal A, Das C, Shamim SA. Incidentally detected penile metastases in a patient of carcinoma urinary bladder on follow-up FDG PET/CT. Clin Nucl Med 2017;42:e273–4. https://doi.org/10.1097/RLU.0000000000001607.
[100] Xing DT, Yilmaz H, Hettige S, Hegde R, Nair R. Successful treatment of malignant priapism by radiotherapy: report of a case, review of the literature, and treatment recommendations. Cureus 2021;13:e17287. https://doi.org/10.7759/cureus.17287.
[101] Ben-Yosef R, Kapp DS. Cancer metastatic to the penis: treatment with hyperthermia and radiation therapy and review of the literature. J Urol 1992;148:67–71.
[102] Gomez-Iturriaga A, Crook J, Evans W, Saibishkumar EP, Jezioranski J. The efficacy of hyperbaric oxygen therapy in the treatment of medically refractory soft tissue necrosis after penile brachytherapy. Brachytherapy 2011;10:491–7.
[103] Stroie FA, Houlihan MD, Kohler TS. Sexual function in the penile cancer survivor: a narrative review. Transl Androl Urol 2021;10:2544–53.
[104] Delaunay B, Soh PN, Delannes M, Riou O, Malavaud B, Moreno F, et al. Brachytherapy for penile cancer: efficacy and impact on sexual function. Brachytherapy 2014;13:380–7.
[105] Gambachidze D, Lebacle C, Maroun P, Escande A, Bossi A, Blanchard P, et al. Long-term evaluation of urinary, sexual, and quality of life outcomes after brachytherapy for penile carcinoma. Brachytherapy 2018;17:221–6.
[106] de Vries HM, Chipollini J, Slongo J, Boyd F, Korkes F, Albersen M, et al. Outcomes of perineal urethrostomy for penile cancer: a 20-year international multicenter experience. Urol Oncol 2021;39:500.e9–13. https://doi.org/10.1016/j.urolonc.2021.04.023.
[107] Johnstone PA. Impact of radiation therapy on perineal urethrostomy for penile cancer. Clinical and Translational Radiation Oncology 2021;30:80–7.
[108] Chen MF, Chen WC, Wu CT, Chuang CK, Ng KF, Chang JT. Contemporary management of penile cancer including surgery and adjuvant radiotherapy: an experience in Taiwan. World J Urol 2004;22:60–6.
[109] Ravi R. Radiation-induced carcinoma of the penis. Urol Int 1995;54:147–9.
[110] Wells AD, Pryor JP. Radiation-induced carcinoma of the penis. Br J Urol 1986;58:325–6.
[111] Heideman DA, Waterboer T, Pawlita M, Delis-van Diemen P, Nindl I, Leijte JA, et al. Human papillomavirus-16 is the predominant type etiologically involved in penile squamous cell carcinoma. J Clin Oncol 2007;25:4550–6.
[112] Olesen TB, Sand FL, Rasmussen CL, Albieri V, Toft BG, Norrild B, et al. Prevalence of human papillomavirus DNA and

p16^{INK4a} in penile cancer and penile intraepithelial neoplasia: a systematic review and meta-analysis. Lancet Oncol 2019; 20:145—8.
[113] Kidd LC, Chaing S, Chipollini J, Giuliano AR, Spiess PE, Sharma P. Relationship between human papillomavirus and penile cancer—implications for prevention and treatment. Transl Androl Urol 2017;6:791—802.
[114] Bezerra AL, Lopes A, Santiago GH, Ribeiro KC, Latorre MR, Villa LL. Human papillomavirus as a prognostic factor in carcinoma of the penis: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. Cancer 2001; 91:2315—21.
[115] Wiener JS, Effert PJ, Humphrey PA, Yu L, Liu ET, Walther PJ. Prevalence of human papillomavirus types 16 and 18 in squamous-cell carcinoma of the penis: a retrospective analysis of primary and metastatic lesions by differential polymerase chain reaction. Int J Cancer 1992; 50:694—701.
[116] Lont AP, Kroon BK, Horenblas S, Gallee MP, Berkhof J, Meijer CJ, et al. Presence of high-risk human papillomavirus DNA in penile carcinoma predicts favorable outcome in survival. Int J Cancer 2006;119:1078—81.
[117] Djajadiningrat RS, Jordanova ES, Kroon BK, van Werkhoven E, de Jong J, Pronk DT, et al. Human papillomavirus prevalence in invasive penile cancer and association with clinical outcome. J Urol 2015;193:526—31.
[118] Sand FL, Rasmussen CL, Frederiksen MH, Andersen KK, Kjaer SK. Prognostic significance of HPV and p16 status in men diagnosed with penile cancer: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2018;27: 1123—32.
[119] Yuan Z, Naghavi AO, Tang D, Ahmed KA, Dhillon J, Giuliano AR, et al. The relationship between HPV status and chemoradiotherapy in the locoregional control of penile cancer. World J Urol 2018;36:1431—40.
[120] Bandini M, Ross JS, Zhu Y, Ye DW, Ornellas AA, Watkin N, et al. Association between human papillomavirus infection and outcome of perioperative nodal radiotherapy for penile carcinoma. Eur Urol Oncol 2021;4:802—10.
[121] Scott JG, Berglund A, Schell MJ, Mihaylov I, Fulp WJ, Yue B, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. Lancet Oncol 2017;18:202—11.
[122] Eschrich S, Zhang H, Zhao H, Boulware D, Lee JH, Bloom G, et al. Systems biology modeling of the radiation sensitivity network: a biomarker discovery platform. Int J Radiat Oncol Biol Phys 2009;75:497—505.
[123] Yuan Z, Yang GQ, Ahmed KA, Torres-Roca JF, Spiess PE, Johnstone PA. Radiation therapy in the management of the inguinal region in penile cancer: what's the evidence? Urol Oncol 2020;40:223—8.
[124] Aydin AM, Chahoud J, Adashek JJ, Azizi M, Magliocco A, Ross JS, et al. Understanding genomics and the immune environment of penile cancer to improve therapy. Nat Rev Urol 2020;17:555—70.
[125] Cosper PF, Bradley S, Luo L, Kimple RJ. Biology of HPV mediated carcinogenesis and tumor progression. Semin Radiat Oncol 2021;31:265—73.
[126] Stewart-Ornstein J, Iwamoto Y, Miller MA, Jambhekar A, Forrester WC, Weissleder R, et al. p53 dynamics vary between tissues and are linked with radiation sensitivity. Nat Commun 2021;12:898. https://doi.org/10.1038/s41467-021-21145-z.
[127] Fenner A. HPV positivity and radiotherapy outcomes in PSCC. Nat Rev Urol 2021;18:4. https://doi.org/10.1038/s41585-020-00411-7.