Evaluation of the Guidelines for Penile Cancer Treatment: Overview and Assessment

Abdulmajeed Aydh,[1,2] Shahrokh F. Shariat,[✉1,3,4,5,6,7,8,9] Reza Sari Motlagh,[1] Ekaterina Laukhtina,[1,9] Fahad Quhal,[1,10] Keiichiro Mori,[1,11] Hadi Mostafaei,[1,12] Andrea Necchi,[13] Benjamin Pradere[1,14]

[1]Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria [2]Department of Urology, King Faisal Medical City, Abha, Saudi Arabia [3]Department of Urology, Weill Cornell Medical College, New York, United States [4]Department of Urology, University of Texas Southwestern, Dallas, United States [5]Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic [6]European Association of Urology Research Foundation, Arnhem, Netherlands [7]Karl Landsteiner Institute, Vienna, Austria [8]Division of Urology, Department of Special Surgery, Jordan University Hospital, The University of Jordan, Amman, Jordan [9]Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia [10]Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia [11]Department of Urology, Jikei University School of Medicine, Tokyo, Japan [12]Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran [13]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy [14]Department of Urology, University Hospital of Tours, Tours, France

Abstract

Introduction Medical organizations have provided evidence-based guidelines for penile cancer treatment. This current review aims to compare and appraise guidelines on penile cancer treatment to provide a useful summary for clinicians.

Materials and Methods We searched in PubMed and Medline for guidelines published between January 1, 2010, and February 1, 2020. The search query terms were "penile cancer," "penile tumor," "guidelines," and "penile malignancy." In the final analysis, we include the most recent versions of relevant guidelines published in English. The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was used to appraise the quality of each guideline.

Results In the final analysis, we included guidelines from the National Comprehensive Cancer Network (updated in 2020), The European Association of Urology (updated in 2018), and The European Society for Medical Oncology (published in 2013). The overall agreement among reviewers was excellent. The range of scores for each domain was as follows: scope and purpose (46% to 61%); stakeholder involvement (33% to 60%); rigor of development (34% to 69%); clarity and presentation (61% to 81%); applicability (33% to 59%) and editorial independence (52% to 78%). The European Association of Urology and National Comprehensive Cancer Network clinical practice guidelines received better scores according to the AGREE II evaluation.

Conclusion Despite the effort made by the guidelines groups to make a practical guideline regarding penile cancer treatment, the actual available evidence is weak. However, we believe our recommendations offer clear guidance.

Introduction

Penile cancer is an aggressive disease that represents less than 1% of all malignancies in the United States and Europe[1,2]. Penile cancer is common in the elderly, with a peak incidence in the seventh decade of life[3]. The most com¬mon histological subtype for penile cancer is squamous cell carcinoma[4]. Given the complex nature of penile cancer, different therapeutic options are available. Furthermore, there is growing interest in molecularly targeted

Key Words

Guidelines, penile cancer, penile malignancy, penile tumor

Competing Interests

None declared.

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Abbreviations

AGREE II Appraisal of Guidelines for Research and Evaluation II
NCCN National Comprehensive Cancer Network
EAU European Association of Urology
ESMO European Society for Medical Oncology
EBRT external beam radiation therapy
PLND pelvic lymph node dissection
LOE level of evidence
GOR grade of recommendation

therapy, and tyrosine kinase inhibitors are showing promising results[5]. However, because of its rarity, most of the recommendations mainly rely on retrospective studies[6,7].

In the last decade, several scientific organizations have provided evidence-based guidelines to improve patients' selection of each treatment modality. The European Association of Urology (EAU) guidelines on Penile Cancer were first published in 2000 and were last updated in 2018. The National Comprehensive Cancer Network (NCCN) penile cancer guidelines were last updated in 2020, while the last European Society for Medical Oncology (ESMO) clinical practice guidelines was released in 2013.

This study aims to conduct a review, comparison, and appraisal of the guidelines on the treatment of penile cancer to provide universal and practical guidance for physicians in their clinical decision-making. We aimed to provide authoritative guidance with clear recommendations from the best guidelines.

Materials and Methods

We searched PubMed and Medline for guidelines published between January 1, 2010, and February 1, 2020. The search terms were "penile cancer," "penile tumor," "guidelines," and "penile malignancy." Also, we searched through the websites of international urology and oncology societies for the most recent guidelines on penile cancer. In the final analysis, we included the most recent English version of each guideline. Non-English national guidelines were excluded. The Appraisal of Guidelines for Research and Evaluation

TABLE 1.
Guidelines for the management penile cancer according to T stage

Treatment	EAU Guidelines			
	Recommendation	Grade of recommendation	Level of evidence	
STAGE Tis				
Topical treatment with 5-fluorouracil (5-FU) or imiquimod	5-FU is an effective first-line treatment	Strong recommendation		
Laser ablation	(Nd:YAG) or Carbon dioxide (CO_2) laser is an effective treatment option	Strong recommendation		
Glans resurfacing	Glans resurfacing, total or partial, can be a primary treatment for PeIN or a secondary	Strong recommendation		
Wide local excision with circumcision	Glans resurfacing, total or partial, can be a primary treatment for PeIN or a secondary			
Mohs surgery	Historical technique			

II (AGREE II) instrument was used to appraise the quality of guidelines[8]. This instrument permits the evaluation of the scope and purpose of the guidelines, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. The overall assessment is the final mean of all domains, which gives an overview of each guideline score. The AGREE II recommends 2 or more appraisers. Therefore, each guideline was evaluated by 5 appraisers (BP, EL, FQ, HM, and KM) to enhance the authenticity of the assessment. The appraisal was performed after the completion of an online training module on AGREE II website[9]. The 5 reviewers were experienced in urologic oncology and were mentored by 2 oncologic urologists (SFS, BP) experienced in guidelines writing and grade of recommendation rating.

Results

Guidelines from 3 international organizations were included in the final analysis: the 2020 update of the NCCN guideline[10], the 2018 update of the EAU guidelines[11], and the 2013 update of the ESMO guidelines[12].

Level of evidence assessment and grading of recommendations

Two guidelines (EAU and NCCN) provided a detailed and strict methodology for searching and acquisition of evidence from the literature. The ESMO guideline is an expert consensus statement so did not include a systematic literature search. All 3 guidelines (EAU, NCCN, and ESMO) provided a description of the systems used for grading the level of evidence. In the EAU guidelines, a modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used[13,14]. For each recommendation within the guidelines, there was also an accompanying online strength rating form, which addresses several elements. The NCCN guidelines used the Categories of Evidence and Consensus to grade the recommendations; they also provide Categories of Preference to help users chose the optimal recommendation based on efficacy, safety, evidence, or affordability.

The ESMO guidelines adapted the Infectious Diseases Society of America-United States Public Health Service Grading System[15].

	NCCN Guidelines			ESMO Guidelines		
	Recommendation	Grade of recommendation	Level of evidence	Recommendation	Grade of recommendation	Level of evidence
	Tis, Ta, and T1 penile cancer lesions may be amenable to conservative penile organ-sparing approaches, including topical therapy	Considered appropriate	**2A**	Penile-preserving techniques, including topical therapy (5% 5-fluorouracil and 5% imiquimod cream)	**C**	IV
	The use of therapeutic lasers to treat selected primary penile tumors has been reported with acceptable outcomes	Considered appropriate	**2B**	Laser therapy using CO2 or Nd: YAG laser	**C**	III
	Glansectomy, removal of the glans penis, may be considered for patients with distal tumors	Considered appropriate	**2B**	Partial/total glans resurfacing	**C**	III
	Penile tumors of the shaft may be treated with wide local excision, with or without circumcision	Considered appropriate	**2A**	Wide local excision and circumcision	**C**	IV
	Mohs surgery is an alternative to wide local excision in select cases		**2B**			

continued on ***page 174***

TABLE 1.
Guidelines for the management penile cancer according to T stage, *Cont'd*

Treatment	EAU Guidelines			
	Recommendation	Grade of recommendation	Level of evidence	
STAGE Ta, T1a (G1, G2)				
Wide local excision with circumcision	Partial glansectomy or total glansectomy with reconstruction are surgical options	Strong recommendation		
Glans resurfacing	Partial glansectomy or total glansectomy with reconstruction are surgical options	Strong recommendation		
Glansectomy with reconstruction	Partial glansectomy or total glansectomy with reconstruction are surgical options	Strong recommendation		
Radiotherapy	External beam radiotherapy or brachytherapy is radiotherapeutic options	Strong recommendation	**2B**	
Laser ablation	Small lesions can also be treated by laser therapy	Strong recommendation		
Partial penectomy		Strong recommendation		
Mohs surgery		Strong recommendation		
STAGE T1B (G3) AND T2				
Wide local excision plus reconstruction	Local excision, partial glansectomy or total glansectomy with reconstruction are surgical options	Strong recommendation		
Glansectomy with circumcision and reconstruction	Local excision, partial glansectomy or total glansectomy with reconstruction are surgical options	Strong recommendation		
Radiotherapy	External beam radiotherapy or brachytherapy is radiotherapeutic options	Strong recommendation		
Total penectomy OR Partial	Total glansectomy, with or without resurfacing of the corporeal heads, is recommended	Strong recommendation		

	NCCN Guidelines			ESMO Guidelines		
	Recommendation	Grade of recommendation	Level of evidence	Recommendation	Grade of recommendation	Level of evidence
	Penile tumors of the shaft may be treated with wide local excision, with or without circumcision	Considered appropriate	**2A**	Penile-preserving techniques, including wide local excision plus reconstructive surgery	**C**	III
	Glansectomy may be considered for select patients with distal tumors	Considered appropriate	**2B**			
	Glansectomy is not recommended unless required to ensure complete tumor eradication with negative margins	Considered appropriate	**2A**			
	Consider <4 cm: Brachytherapy or EBRT >4 cm: EBRT with chemotherapy	Considered appropriate	**2B**	Radiotherapy delivered as EBRT or brachytherapy with interstitial implant	**C**	IV
	The use of therapeutic lasers to treat selected primary penile tumors has been reported with acceptable outcomes	Considered appropriate	**2B**	Laser therapy	**C**	IV
	Partial or total penectomy when invasion into the corpora cavernosum is necessary to achieve a negative margin	Considered appropriate	**2A**			
	Mohs surgery is an alternative to wide local excision in select cases.	Considered appropriate	**2B**			
	Penile tumors of the shaft may be treated with wide local excision	Considered appropriate	**2A**	If tumor <50% of the glans and no invasion of the corpora cavernosa	**B**	III
	Glansectomy may be considered for select patients with distal tumors	Considered appropriate	**2A**	If tumor <50% of the glans and no invasion of the corpora cavernosa	**B**	III
	Consider <4 cm: Brachytherapy or EBRT >4 cm: EBRT with chemotherapy	Considered appropriate	**2B**	<4 cm: Brachytherapy or EBRT >4 cm: EBRT with chemotherapy		III
	Partial or total penectomy when invasion into the corpora cavernosum is necessary to achieve a negative margin	Considered appropriate	**2A**	Tumors with invasion into corpora cavernosa	**B**	III

continued on ***page 176***

TABLE 1.
Guidelines for the management penile cancer according to T stage, *Cont'd*

Treatment	EAU Guidelines			
	Recommendation	Grade of recommendation	Level of evidence	
STAGE T2				
Total glansectomy	Total glansectomy, with or without resurfacing of the corporeal heads, is recommended	Strong recommendation	**3**	
Radiotherapy	Radiation therapy is an option	Strong recommendation		
Total penectomy OR Partial	Partial amputation should be considered in patients unfit for reconstructive surgery	Strong recommendation		
STAGE T3				
Partial amputation with reconstruction or total penectomy	Glansectomy with distal corporectomy and reconstruction or partial amputation with reconstruction are standard	Strong recommendation		
Radiotherapy	Radiation therapy is an option	Strong recommendation		
STAGE T3 WITH INVASION OF THE URETHRA				
Partial penectomy or total penectomy	Glansectomy with distal corporectomy and reconstruction or partial amputation with reconstruction are standard	Strong recommendation		
Radiotherapy	Radiation therapy is an option	Strong recommendation		
STAGE T4				
Partial penectomy or total penectomy	Extensive partial amputation or total penectomy with perineal urethrostomy is the standard advisable treatment	Weak recommendation		
Radiotherapy	Palliative radiotherapy is an option			

	NCCN Guidelines			ESMO Guidelines		
	Recommendation	Grade of recommendation	Level of evidence	Recommendation	Grade of recommendation	Level of evidence
					C	III
	Consider <4 cm: Brachytherapy or EBRT >4 cm: EBRT with chemotherapy	Considered appropriate	**2B**	<4 cm: Brachytherapy or EBRT >4 cm: EBRT with chemotherapy	**D**	
	Partial or total penectomy when invasion into the corpora cavernosum is necessary to achieve a negative margin	Considered appropriate	**2A**	Tumors with invasion into corpora cavernosa	**B**	III
	Partial or total penectomy when invasion into the corpora cavernosum is necessary to achieve a negative margin	Considered appropriate	**2A**	T3-4 or N+: circumcision followed by EBRT with chemotherapy	**D**	
	EBRT with chemotherapy are treatment options	Considered appropriate	**3**			
	Partial or total penectomy when invasion into the corpora cavernosum is necessary to achieve a negative margin	Considered appropriate	**2A**	T3-4 or N+: circumcision followed by EBRT with chemotherapy	**D**	
	EBRT with chemotherapy are treatment options	Considered appropriate	**2B**			
	Partial or total penectomy when invasion into the corpora cavernosum is necessary to achieve a negative margin	Considered appropriate	**2A**	T3-4 or N+: circumcision followed by EBRT with chemotherapy	**D**	
	EBRT with chemotherapy are treatment options	Considered appropriate	**3**			

TABLE 2.
Author recommendations for penile cancer guidelines

	Topical	Laser	Surgery	Radiotherapy
Tis	5-**fluorouracil (5FU)** or **imiquimod** 5% for superficial lesions ± photo dynamic control	**Tis → T2 glans** Laser ablation with **CO2** or **Nd**:YAG laser	• **Glans resurfacing** (Removal of glans epithelium) for lesions confined to glans • **Glansectomy** (Leaving corpora intact compared to partial penectomy) • **Circumcision** for lesions confined to prepuce • **Wide local excision** + reconstruction ± skin **grafting**	
Ta, T1 & T2 confined to the glans	X			**Ta → T2 Radiotherapy by** • External beam • **(EBRT)** or as • **Brachytherapy**
T2 → Corpora cavernosa (CC)	X	X	• **Partial** penectomy + reconstruction	
T3 (Three) invasion of → Urethra	X	X	• **Partial** penectomy • **Total** penectomy with perineal urethrostomy	
T4 → Adjacent structures	X	X	• **Neoadjuvant chemo + surgery** in responders	or **Palliative EBRT**

Nodal metastases				
No palpable inguinal nodes		**Palpable (cN1/cN2)**	**Fixed (cN3)**	**Pelvic lymphadenopathy**
Tis, Ta G1, T1G1	**> T1G2**	**Radical inguinal lymphadenectomy**	**Neoadjuvant chemotherapy** ± followed in responders by **Radical inguinal lymphadenectomy**	**Ipsilateral** pelvic lymphadenectomy if **(pN2) ≥ 2 inguinal** nodes are involved on **one side** and if **(pN3) Extracapsular nodal** metastasis
Surveillance	Staging by ***Dynamic sentinel node biopsy***			

Chemotherapy	
• Neoadj.: **T4**, fixed **N3** • Adjuvant: **pN2/pN3**	**Adjuvant chemo** in **pN2/pN3** patients after radical lymphadenectomy 3–4 cycles of **TPF**: ***paclitaxel, cisplatin, 5-fluorouracil (5FU)***

Treatment strategy according to stage

Organ-sparing treatment in Tis, Ta, and T1a tumors

All 3 guidelines (EAU, NCCN, and ESMO), advise organ-sparing approaches in patients diagnosed with Tis, Ta, and T1 penile cancer lesions. However, the EAU guidelines highlight the absence of randomized controlled trials or comparative observational studies for treatment options for localized penile cancer. Nevertheless, from a cosmetic and functional standpoint, balanced with the risk of recurrence and progression of these stages, penile preservation is considered superior to partial or total penectomy and should be performed for localized penile cancer (staged ≤ T1)[16].

Topical agents are the least invasive and easiest treatment options for superficial and localized lesions.

Before their use, the EAU guidelines recommend performing a circumcision. The EAU and NCCN guidelines make clear that there is a requirement for long-term surveillance. Another option is laser therapy, which could be performed as day-case surgery. When laser therapy is performed, the EAU guidelines mandate a second biopsy before treatment is initiated. A partial or total glans resurfacing can be an alternative in the first-line treatment for penile intraepithelial lesions (PeIN) or could be proposed after topical or laser therapy failure. In the case of wide local excision, Mohs surgery can be proposed in selected cases according to the EAU and NCCN guidelines (Table 1).

Summary of treatment recommendations: For patients with penile Tis or Ta, we recommend topical therapy[17,18] and excisional organ-sparing technique[19], a topical agent such as imiquimod (5%) or 5-fluorouracil (5FU) cream, circumcision and wide local excision, laser therapy, or complete glansectomy (Table 2).

Invasive disease treatment confined to the glans T1/T2

For T1 and T2 tumors localized to the glans, the 3 guidelines proposed different strategies, including surgery with laser therapy, local excision, partial glansectomy, or total glansectomy, and radiotherapy or brachytherapy. For the treatment of invasive disease confined to the glans, the EAU and the ESMO guidelines agree on conservative approaches, such as wide local excision or glansectomy, while the NCCN guidelines recommended it only in T1 high grade (G3–4).

For radiotherapy, the NCCN and the EAU guidelines recommended brachytherapy or external beam radiation therapy (EBRT) for tumors less than 4 cm. A circumcision is mandated by the NCCN guidelines before radiotherapy (RT) to prevent radiation-related complications. For tumors larger than 4 cm, a multimodal treatment combining radiotherapy and chemotherapy is recommended (Table 1).

Summary of treatment recommendations: Our recommendation for the treatment of invasive disease confined to the glans is a glansectomy with or without resurfacing with a partial thickness skin graft of the corporeal heads[20]. A partial amputation for patients who are not candidates for reconstructive surgery should be performed[21]. Radiotherapy may also be an option[22] (Table 2).

Treatment of invasive disease T3/T4

For tumors with invasion of the corpora cavernosum, a partial or total penectomy is mandatory to achieve a total resection with negative margin according to the NCCN and the EAU guidelines. EBRT with concurrent chemotherapy is also an option in the NCCN guidelines, while it is the primary treatment in the ESMO guidelines. The EAU guidelines consider radiation as a treatment option only for T3 and as a palliative treatment in T4 disease (Table 1).

Summary of treatment recommendations: For the treatment of cT3, we recommend glansectomy with corporectomy and reconstruction or partial penectomy with reconstruction as a standard of care[23,24]. Total penectomy with perineal urethrostomy is considered in selected cases. For cT4 disease, the recommended treatment remains a total penectomy with perineal urethrostomy[24]. Neoadjuvant chemotherapy for the locally advanced disease should be systematically considered and proposed[25,26] (Table 2).

Guidelines for treatment strategies for nodal metastases: cN0

The ESMO, NCCN, and EAU guidelines all recommend surveillance for Tis, Ta G1, and T1G1 stages. Invasive lymph node staging either by bilateral modified inguinal lymphadenectomy or by dynamic sentinel node biopsy is recommended for ≥ T1G2 (Table 3). There is currently no role for prophylactic radiation to the inguinal lymph nodes instead of lymph node dissection or biopsy[27].

Summary of treatment recommendations: There are considerable discussions among researchers in the management of cN0 disease. Nonetheless, we believe that it is justified to recommend surveillance for Tis, Ta G1, and T1G1 if the patient is compliant[28]. In contrast, at least a dynamic sentinel node biopsy should be recommended to improve the outcome for ≥ T1G2 disease[29] (Table 2).

Guidelines for treatment strategies for nodal metastases: cN1/cN2

All 3 guidelines recommend a radical inguinal lymphadenectomy for clinically positive lymph nodes. The confirmation of clinically positive lymph nodes should be made by surgical resection and frozen section according to the EAU guidelines, while, according to the NCCN, the confirmation can be made by percutaneous biopsy, or by fine-needle aspiration (FNA) in the ESMO guidelines (Table 3).

Summary of treatment recommendations: Radical inguinal lymphadenectomy seems to improve survival and should be recommended for every patient with cN1/N2[30] (Table 2).

Guidelines for treatment strategies for nodal metastases: cN3

For fixed inguinal nodal mass or pelvic lymphadenopathy (cN3), neoadjuvant chemotherapy

TABLE 3.
Guidelines for the management of nodal metastasis and adjuvant therapy for penile cancer

EAU Guidelines			NCCN Guidelines			
Recommendation	**Grade of recommendation**	**Level of evidence**	**Recommendation**	**Grade of recommendation**	**Level of evidence**	
STAGE CN0						
Surveillance is only recommended in patients with pTis/pTa tumors	Strong recommendation		Most low-risk patients are followed with a surveillance as the probability of occult micro metastases in ILNs is low	Considered appropriate	**2A**	
> T1G2: invasive lymph node staging is recommended by either bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy	Strong recommendation	**2B**	For high-risk standard or modified ILND or DSNB is strongly recommended in high-risk	Considered appropriate	**2A**	
STAGE CN1/CN2						
A radical inguinal lymphadenectomy should be performed	Strong recommendation	**2B**	Percutaneous lymph node biopsy is considered standard Positive findings warrant an immediate ILND		**2A**	
STAGE CN3						
Multimodal treatment with neoadjuvant chemotherapy followed by radical lymphadenectomy in responders is recommended	Weak recommendation		Should receive neoadjuvant Chemotherapy followed by radical inguinal and PLND lymphadenectomy in responders	Considered appropriate	**2A**	
			Consider postoperative radiotherapy or chemoradiotherapy		**2B**	
STAGE PELVIC LYMPH NOD						
Patients with 2 or more inguinal lymph node metastases on one side and/or extracapsular lymph node extension need to undergo ipsilateral pelvic lymphadenectomy	Strong recommendation	**2B**	PLND should be considered at the time or following ILND in patients with ≥ three positive inguinal nodes on the ipsilateral ILND site	Considered appropriate	**2A**	
			Bilateral PLND should be considered either at the time or following ILND in patients with ≥4 positive inguinal nodes	Considered appropriate	**2A**	

	ESMO Guidelines		
	Recommendation	Grade of recommendation	Level of evidence
	Low- risk (Tis, Ta, T1G1) and intermediate-risk (T1G2) are followed with surveillance	**B**	
	DSNB is recommended in patients with non-palpable inguinal lymph nodes T1G2 or greater	**B**	
	Fine-needle aspiration (FNA) of the LN is standard for these patients (omitting the procedure for high-risk tumors to avoid delay of ILND)		
	Patients with fixed nodes should be considered for neoadjuvant chemoradiotherapy	**C**	III
	Responders receive consolidation surgery (bilateral and deep ILND and ipsilateral PLND if possible)		
	Patients with fixed nodes should be considered for neoadjuvant chemoradiotherapy	**C**	III
	Responders receive consolidation surgery (bilateral and deep ILND and ipsilateral PLND if possible)		

continued on ***page 182***

followed by a radical lymphadenectomy is supported by both NCCN and EAU guidelines. The ESMO guidelines recommend a multimodal treatment including chemo-radiotherapy followed by consolidation surgery (inguinal lymph node dissection [ILND] and ipsilateral pelvic lymph node dissection [PLND]). This treatment regimen is one of the options in the NCCN guidelines but is considered only as a palliative treatment in the EAU guidelines (Table 3).

> **Summary of treatment recommendations:** For cN3, we recommend a radical lymphadenectomy after neoadjuvant chemotherapy for every responder to improve disease-free survival[25] (Table 2).

Enlarged pelvic lymph nodes

For surgically resectable lesions, all 3 guidelines recommend neoadjuvant systemic chemotherapy, followed by unilateral/bilateral PLND in case of treatment response. The EAU guidelines recommend lymphadenectomy for ipsilateral PLND if 2 or more inguinal lymph nodes are affected on one side or if extracapsular nodal metastasis is reported, followed by adjuvant chemotherapy. For enlarged pelvic lymph nodes where surgery is not possible, the NCCN and the ESMO guidelines recommend chemo-radiotherapy (Table 3).

> **Summary of treatment recommendations:** PLND is recommended for patients with 2 or more inguinal lymph nodes affected on one side or if extra-nodal extension is found[31] (Table 2).

Guidelines for chemotherapy

Both the EAU and ESMO guidelines state that neoadjuvant chemotherapy followed by radical surgery is advisable in unresectable lymph node metastases. The NCCN guidelines recommend neoadjuvant chemotherapy in patients with ≥ 4 cm inguinal lymph nodes (fixed or mobile). The EAU and ESMO guidelines recommend adjuvant chemotherapy after lymphadenectomy in patients with pN2/pN3 disease. In contrast, the NCCN guidelines recommended adjuvant chemotherapy only if it was not given preoperatively, and if the pathology shows high-risk features (Tables 3,4).

> **Summary of treatment recommendations:** A neoadjuvant chemotherapy should be proposed systematically for patients with cN3 inguinal lymph nodes and discussed for all clinical lymph nodes ≥ 4cm. An adjuvant chemotherapy should be offered to patients with pN2/pN3 disease without previous systemic treatment. Three to 4 cycles of paclitaxel, cisplatin, 5-fluorouracil (5FU) are the recommended regimen[32–34] (Table 2).

TABLE 3.
Guidelines for the management of nodal metastasis and adjuvant therapy for penile cancer, *Cont'd*

EAU Guidelines			NCCN Guidelines			
Recommendation	**Grade of recommendation**	**Level of evidence**	**Recommendation**	**Grade of recommendation**	**Level of evidence**	
STAGE CHEMOTHERAPY						
Neoadjuvant chemotherapy using cisplatin- and the taxane-based triple combination should be used in patients with fixed, unresectable, nodal disease	Strong recommendation	**2A**	Neoadjuvant chemotherapy with TIP (paclitaxel, ifosfamide, and cisplatin) is preferred (prior to ILND) in patients with ≥4 cm inguinal lymphnodes (fixed or mobile)	Considered appropriate	**2A**	
	Strong recommendation	**2B**	Adjuvant chemotherapy it is reasonable to give four courses of TIP in the adjuvant setting if it was not given preoperatively and the pathology shows high-risk features		**2A**	
STAGE RADIOTHERAPY						
Not recommended for nodal disease except as a palliative option	Strong recommendation		Adjuvant EBRT or chemoradiotherapy can also be considered for patients with high-risk features	Considered appropriate	**2B**	

TABLE 4.
Guidelines of chemotherapy regimen for penile cancer

EAU Guidelines			NCCN Guidelines			
Treatment	**Grade of recommendation**	**Level of evidence**	**Treatment**	**Grade of recommendation**	**Level of evidence**	
NEOADJUVANT CHEMOTHERAPY						
(4 cycles) cisplatin- and taxane-based regimen	Weak	**2A**	(4 courses) TIP (paclitaxel, ifosfamide, and cisplatin)	**2A**	Considered appropriate	
ADJUVANT CHEMOTHERAPY						
(3 to 4 cycles) cisplatin, a taxane and 5-fluorouracil or ifosfamide	Strong	**2B**	(4 courses) Preferred regimen is TIP (paclitaxel, ifosfamide, and cisplatin) Other recommended regimen is 5- fluorouracil + cisplatin	**2A**	Considered appropriate	

	ESMO Guidelines		
	Recommendation	Grade of recommendation	Level of evidence
	Neoadjuvant chemotherapy followed by radical surgery is advisable in unresectable or recurrent LN metastases	C	
	Adjuvant chemotherapy is recommended in pN2-3 patients	C	
	The role of adjuvant postoperative radiation is controversial		

	ESMO Guidelines		
	Treatment	Grade of recommendation	Level of evidence
	(4 courses) TIP (paclitaxel, ifosfamide, and cisplatin)	C	III
	No clear recommendation		

Guidelines for Adjuvant Radiotherapy

NCCN guidelines indicate that adjuvant EBRT or chemo-radiotherapy can be considered for patients with high-risk features, but the EAU guidelines do not recommend it except for palliative treatment. According to the ESMO guidelines, the role of adjuvant radiotherapy in the management of penile cancer remains controversial (Tables 3,4).

Summary of treatment recommendations: Adjuvant radiotherapy is recommended after PLND for patients with positive results in ILND[35,36].

Assessment of the quality of the guidelines with the AGREE II instrument

The AGREE Instrument is a 23-item tool comprising 6 quality and 2 overall assessment domains. A unique dimension of guideline quality is captured in each domain. Table 3 shows the results of the guidelines appraisal by the 5 reviewers. For the Domain 1 scope and purpose, which is related to the specific health questions, the overall aim of the guideline, and the target population, EAU and NCCN both scored 61%, while ESMO scored only 46%. Concerning the stakeholder involvement focuses on the extent to which the guidelines were developed by the appropriate stakeholders, the lowest score was 33% for ESMO, while EAU and NCCN reached approximately the same score with 59% and 60%, respectively. Regarding rigor of development concerned with the approaches to formulate the recommendations and the process used to gather and make the evidence and to update them, the appraiser gave the best score to the EAU and NCCN guidelines with 69% and 61%, respectively; while the ESMO, with a score of 34% did not reach the expected standard. With respect to structure, language, format, and clarity of presentation, the NCCN had a score of 81%, followed by the EAU, with 77%, and the ESMO with 61%. Resource implications of applying the guideline, strategies to improve uptake, and applicability pertaining to the likely barriers to and facilitators of implementation were scored at 33%, 53%, and 59% for the ESMO, NCCN, and EAU guidelines, respectively. For editorial independence, which concerns there being no competing interests that might bias the formulation of recommendations, the scores were 78% for the EAU guidelines, 57% for the ESMO guidelines, and 52% for the NCCN guidelines. Overall assessment includes rating the recommendation of guidelines for practice use and the overall quality of the guidelines. The highest score was reached by the EAU guidelines with a total rate of 77%, and the lowest score by the ESMO guidelines with a rate of 40%, while the NCCN guidelines also reached a high rate with 73% (Table 5).

TABLE 5.

AGREE II evaluation of guidelines for the management of penile cancer

Scope and purpose %	Stakeholder involvement %	Rigor of development %	Clarity of presentation %	Applicability %	Editorial independence %	Overall assessment %	Final recommendations
EAU GUIDELINES							
61	59	6	77	59	78	77	Yes–3, Yes with modifications–2, No–0
NCCN GUIDELINES							
6	60	61	81	53	52	73	Yes–3, Yes with modifications–2, No–0
ESMO GUIDELINES							
46	33	34	61	33	57	40	Yes–0, Yes with modifications–2, No–3

Discussion

Clinical guidelines help physicians to choose the best treatment available for individual patients. Fewer guidelines are available in the case of rare diseases, and only 3 guidelines in English have been published on the management of penile cancer. The recommendations made in these guidelines are not always in agreement. Therefore, to help urologists in their decision-making process regarding therapy, we evaluated and compared the guidelines of the NCCN, EAU, and ESMO on the management of penile cancer. Using the AGREE II tool, we assessed the quality of the guidelines. We discuss the differences in terms of LOE and GOR that arise as a result of different methods of evaluation used. The EAU and NCCN guidelines incorporate more recent literature than the ESMO guidelines, which have not been updated for 7 years.

The EAU guidelines use a modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. For each recommendation within the guidelines, there is an accompanying online strength rating form that addresses several elements. The ESMO adapted the Infectious Diseases Society of America-United States Public Health Service Grading System. The level of evidence assessment and grading of recommendations in NCCN guidelines are based on randomized controlled trials, clinical trials, guidelines, systematic reviews, meta-analysis, and validation studies. Evaluation of LOE and GOR are more specified clearly in the NCCN guidelines than in the other 2 guidelines. Although these 3 guidelines developed in different ways, it is reassuring that they have considerable similarities, albeit some small but potentially significant differences between them. The evidence available is weak in penile cancer, and a consequence of the scarcity in evidence is that way, some recommendations are based on the panel's review of the low-level evidence and expert opinion.

One of the contentious points is the advantage of both neoadjuvant and adjuvant radiotherapy in the treatment of penile cancer patients with LN metastases. There is some evidence for adjuvant nodal radiotherapy in in vulvar carcinoma, which shares many characteristics with penile cancer[37,38]. However, high-quality evidence to suggest a clear benefit to radiotherapy in penile cancer is lacking[39,40]. In a retrospective study of 2458 patients in the SEER database (National Cancer Institute Surveillance, Epidemiology and End Results Program), no advantage was observed with the use of EBRT for penile cancer patients compared to surgery alone on cancer-specific survival[41]. A similar conclusion was reached by Franks et al., who reported poor long-term survival for patients treated with adjuvant radiotherapy[42]. These essential findings are consistent with those of other studies, which showed no patient benefit[43,44–48]. However, A series of recent studies have indicated that adjuvant radiotherapy improved survival and decreased recurrence rate[35,36,49].

Conclusion

This is the first attempt to review and appraise guidelines for penile cancer management systematically. Although all guidelines strive to be evidence-based, some recommendations differ between the guidelines because the underlying evidence is poor. Also, these guidelines are produced in the United States and Europe, so that their applicability in other regions with a high incidence of penile cancer is uncertain. This point may encourage organizations in other areas to produce their own guidelines. The best way to improve the guidelines is to conduct more prospective trials to strengthen the data underlying the recommendations.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.*2020;70(1):7–30.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.*2018;68(6):394–424.
3. Bleeker MC, Heideman DAM, Snijders PJF, Horenblas S, Dillner J, Meijeret CLM. Penile cancer: epidemiology, pathogenesis and prevention. *World J Urol.*2009;27(2):141–150. doi: 10.1007/s00345–008–0302-z. Epub 2008 Jul 8.
4. Chipollini J, Tang DH, Sharma P, Spiess PE. National trends and predictors of organ-sparing for invasive penile tumors: expanding the therapeutic window. *Clin Genitourin Cancer.*2018;16(2):e383-e389. doi: 10.1016/j.clgc.2017.09.004. Epub 2017 Sep 8.
5. Resch I, Abufaraj M, Hübner NA, Shariat SF. An update on systemic therapy for penile cancer. *Curr Opin Urol.*2020;30(2):229–233. doi: 10.1097/MOU.0000000000000733.
6. Adashek JJ, Necchi A, Spiess PE. Updates in the molecular epidemiology and systemic approaches to penile cancer. *Urol Oncol.*2019;37(7):403–408.
7. Necchi A. Systemic Therapy for penile cancer. *Eur Urol Suppl.*2018;17(6):160–163.
8. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al.; AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ.*2010;182(18):E839–842. doi: 10.1503/cmaj.090449. Epub 2010 Jul 5.
9. Practice, A.A.t.S.o. and Guidelines. AGREE website. Available from: https://www.agreetrust.org/. Accessed March 26 2021.
10. National Comprehensive Cancer Network. Penile Cancer (Version 1.2020). 2020; Available from: https://www.nccn.org/professionals/physician_gls/pdf/penile.pdf. Accessed March 26 2021.
11. Hakenberg OW, Compérat E, Minhas S, Necchi A, Protzel C, Watkin N, Robinson R. EAU Guidelines on Penile Cancer 2018, in European Association of Urology Guidelines. 2018 Edition. 2018, European Association of Urology Guidelines Office: Arnhem, The Netherlands. Available from: https://uroweb.org/guideline/penile-cancer/. Accessed March 26, 2021.
12. Van Poppel H, Watkin NA, Osanto S, Moonen L, Horwich A, Kataja V; ESMO Guidelines Working Group. Penile cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.*2013;24(Suppl) 6:vi115–124. doi: 10.1093/annonc/mdt286.
13. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; for the GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.*2008;336(7650):924–926. 336 doi: https://doi.org/10.1136/bmj.39489.470347.AD
14. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ.*2008; 336(7651):995–998. doi: 10.1136/bmj.39490.551019.BE.
15. Dykewicz CA, Centers for Disease Control and Prevention (U.S.); Infectious Diseases Society of America; American Society of Blood and Marrow Transplantation. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis.*2001;33(2):139–144. doi: 10.1086/321805. Epub 2001 Jun 14.
16. Raskin Y, Vanthoor J, Milenkovic U, Muneer A, Albersen M. Organ-sparing surgical and nonsurgical modalities in primary penile cancer treatment. *Curr Opin Urol.*2019 Mar;29(2):156–164. doi: 10.1097/MOU.0000000000000587.
17. Choi JW, Choi M, Cho KH. A case of erythroplasia of queyrat treated with imiquimod 5% cream and excision. *Ann Dermatol.*2009;21(4):419–422.
18. Schroeder TL, Sengelmann RD. Squamous cell carcinoma in situ of the penis successfully treated with imiquimod 5% cream. *J Am Acad Dermatol.*2002;46(4):545–548.
19. Feldman AS, McDougal WS. Long-term outcome of excisional organ sparing surgery for carcinoma of the penis. *J Urol.*2011;186(4):1303–1307.
20. Azrif M, Logue JP, Swindell R, Cowan RA, Wylie JP, Livsey JE. External-beam radiotherapy in T1–2 N0 penile carcinoma. *Clin Oncol (R Coll Radiol).*2006;18(4):320–325. doi: 10.1016/j.clon.2006.01.004.
21. Smith Y, Hadway P, Biedrzycki O, Perry MJA, Corbishley C, Watkin NA. Reconstructive surgery for invasive squamous carcinoma of the glans penis. *Eur Urol.*2007;52(4):1179–1185. doi: 10.1016/j.eururo.2007.02.038. Epub 2007 Feb 20.
22. Crook J, Ma C, Grimard L. Radiation therapy in the management of the primary penile tumor: an update. *World J Urol.*2009;27(2):189–196.
23. Gotsadze D, Matveev B, Zak B, Mamaladze V. Is conservative organ-sparing treatment of penile carcinoma justified? *Eur Urol.*2000;38(3):306–312. doi: 10.1159/000020298.

24. Ornellas AA, Kinchin EW, Nóbrega BLB, Wisnescky A, Koifman N, Quirino R. Surgical treatment of invasive squamous cell carcinoma of the penis: Brazilian National Cancer Institute long-term experience. *J Surg Oncol.*2008;97(6):487–495. doi: 10.1002/jso.20980.

25. Pizzocaro G. Piva L. Adjuvant and neoadjuvant vincristine, bleomycin, and methotrexate for inguinal metastases from squamous cell carcinoma of the penis. *Acta Oncol.*1988;27(6b):823–824.

26. Leijte JA, Kerst JM, Bais E, Antonini N, Horenblas S. Neoadjuvant chemotherapy in advanced penile carcinoma. *Eur Urol.*2007;52(2):488–494. doi: 10.1016/j.eururo.2007.02.006. Epub 2007 Feb 14.

27. Meijer RP, Boon TA, van Venrooij GE, Wijburg CJ. Long-term follow-up after laser therapy for penile carcinoma. *Urology.*2007;69(4):759–762. doi: 10.1016/j.urology.2007.01.023.

28. Zou ZJ, Liu Z-H, Tang L-Y, Wang Y-J, Liang J-Y, Zhang R-C, et al. Radiocolloid-based dynamic sentinel lymph node biopsy in penile cancer with clinically negative inguinal lymph node: an updated systematic review and meta-analysis. *Int Urol Nephrol.*2016;48(12):2001–2013. doi: 10.1007/s11255–016–1405-x. Epub 2016 Aug 30.

29. Hegarty PK, Dinney CP, Pettaway CA. Controversies in ilioinguinal lymphadenectomy. *Urol Clin North Am.*2010;37(3):421–434.

30. Lughezzani G, Catanzaro M, Torelli T, Piva L, Biasoni D, Stagni S, et al. The relationship between characteristics of inguinal lymph nodes and pelvic lymph node involvement in penile squamous cell carcinoma: a single institution experience. *J Urol.*2014;191(4):977–982. doi: 10.1016/j.juro.2013.10.140. Epub 2013 Nov 18.

31. Noronha V, Patil V, Ostwal V, Tongaonkar H, Bakshi G, Prabhash K, et al. Role of paclitaxel and platinum-based adjuvant chemotherapy in high-risk penile cancer. *Urol Ann.*2012;4(3):150–153. doi: 10.4103/0974–7796.102659

32. Giannatempo P, Paganoni A, Sangalli L, Colecchia M, Piva L, Torelli MCT, et al. Survival analyses of adjuvant or neoadjuvant combination of a taxane plus cisplatin and 5-fluorouracil (T-PF) in patients with bulky nodal metastases from squamous cell carcinoma of the penis (PSCC): Results of a single high-volume center. *J Clin Oncol.*2014;32(4,Suppl):377. DOI: 10.1200/jco.2014.32.4_suppl.377.

33. Bandini M, Pederzoli F, Necchi A. Neoadjuvant chemotherapy for lymph node-positive penile cancer: current evidence and knowledge. *Curr Opin Urol.*2020;30(2):218–222. doi: 10.1097/MOU.0000000000000719.

34. 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(2):123–128.

35. Graafland NM, Moonen LMF, 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(3):888–893. doi: 10.1016/j.juro.2010.10.059. Epub 2011 Jan 15.

36. Franks KN, Kiran Kancherla, Brinda Sethugavalar, Peter Whelan, Ian Eardley, Anne E Kiltie, et al. Radiotherapy for node positive penile cancer: experience of the Leeds teaching hospitals. *J Urol.*2011;186(2):524–529. doi: 10.1016/j.juro.2011.03.117. Epub 2011 Jun 22.

37. 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(3):92.e11–92.e16. doi: 10.1016/j.urolonc.2017.11.005. Epub 2017 Nov 27.

38. 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(10):605.e17–605.e23. doi: 10.1016/j.urolonc.2017.06.001. Epub 2017 Jun 27.

39. Homesley HD, Bundy BN, Sedlis A, Adcock L. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. *Obstet Gynecol.*1986;68(6):733–740.

40. Parthasarathy A, Cheung MK, Osann K, Husain A, Teng NN, Berek JS. The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. *Gynecol Oncol.*2006;103(3):1095–9. doi: 10.1016/j.ygyno.2006.06.030.

41. de Vries HM, Ottenhof SR, van der Heijden MS, Pos FJ, Horenblas S, Brouwer OR. Management of the penile squamous cell carcinoma patient after node positive radical inguinal lymph node dissection: current evidence and future prospects. *Curr Opin Urol.*2020;30(2):223–228. doi: 10.1097/MOU.0000000000000714.

42. Crook J. Radiotherapy approaches for locally advanced penile cancer: neoadjuvant and adjuvant.*Curr Opin Urol.*2017;27(1):62–67. doi: 10.1097/MOU.0000000000000346.

43. Burt LM, Shrieve DC, Tward JD. Stage presentation, care patterns, and treatment outcomes for squamous cell carcinoma of the penis. *Int J Radiat Oncol Biol Phys.*2014;88(1):94–100.

44. Ravi R, Chaturvedi HK, Sastry DV. Role of radiation therapy in the treatment of carcinoma of the penis. *Br J Urol.*1994;74(5):646–651.

45. Demkow T. The treatment of penile carcinoma: experience in 64 cases. *Int Urol Nephrol.*1999;31(4):525–531.

46. Chen MF, Chen W-C, Wu C-T, Chuang C-K, Ng K-F, Chang JT-C. Contemporary management of penile cancer including surgery and adjuvant radiotherapy: an experience in Taiwan. *World J Urol.*2004;22(1):60–66.

47. 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(1):68–73. doi: 10.1016/j.juro.2013.07.088.

48. 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(1):76–83.

49. 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.*2020 Nov 29; Online ahead of print. doi: 10.1111/bju.15309.