Guideline Endorsement C50-CIDAP-2

A Quality Initiative of
The Cancer Care Integration & Disease Advisory Program (CI-DAP), Ontario Health (Cancer Care Ontario)

An Endorsement of the 2023 European Association of Urology (EAU) - American Society of Clinical Oncology (ASCO) Guidelines on Penile Cancer

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This document describes the Ontario Health (Cancer Care Ontario) Cancer Care Integration & Disease Advisory Program (CI-DAP) endorsement of the 2023 European Association of Urology (EAU) - American Society of Clinical Oncology (ASCO) Guidelines on Penile Cancer. The original publication is available at https://uroweb.org/guidelines/penile-cancer.

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Please visit the Ontario Health (Cancer Care Ontario) website at https://www.cancercareontario.ca/en/guidelines-advice for the most up-to-date version of all reports.

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Section 1: Guideline Endorsement

GUIDELINE OBJECTIVES

The objectives of this guideline are to provide recommendations on the diagnosis and treatment of penile cancer. The recommendations are based on the 2023 European Association of Urology (EAU) - American Society of Clinical Oncology (ASCO) Guidelines on Penile Cancer [1].

TARGET POPULATION

Patients with a suspected or confirmed penile cancer diagnosis.

INTENDED USERS

The guideline document will support providers in the diagnosis and treatment of patients with penile cancer.

ENDORSEMENT

The Penile Cancer Guidelines Endorsement Development Group (GDG) of Ontario Health (Cancer Care Ontario) (OH (CCO)) endorses the majority of recommendations of the 2023 European Association of Urology (EAU) - American Society of Clinical Oncology (ASCO) Guidelines on Penile Cancer, available at https://uroweb.org/guidelines/penile-cancer, as modified by the endorsement process described in this document. These recommendations are reprinted below with permission from EAU-ASCO, with modifications noted.

36 of the 52 recommendations were endorsed without modifications or comments. 16 of the 52 recommendations were endorsed with changes, which are the consensus opinion of the GDG, as listed in Section 1 Recommendations below.

Section 1 Recommendations: EAU-ASCO Guidelines (Guidelines) on Penile Cancer recommendations [1]

Guidelines Section 3.4.7 Recommendations
3. EPIDEMIOLOGY AETIOLOGY AND PATHOLOGY
3.4.7. Summary of recommendations for pathological assessment of tumour specimens

Recommendation
1. The pathological evaluation of penile carcinoma specimens must include the pTNM (see Chapter 4) stage and an assessment of tumour grade. (Strength rating: Strong)
Assessment
Endorsed

Recommendation
2. The pathological evaluation of penile carcinoma specimens must include an assessment of p16 by immunohistochemistry. (Strength rating: Strong)

Assessment
Endorsed with change
Change
May also consider molecular HPV testing, if available.

Recommendation
3. The pathological evaluation of penile carcinoma specimens should follow the ICCR dataset synoptic report. (Strength rating: Strong)
Assessment
Endorsed with change
Change
Ontario has implemented the College of American Pathologists (CAP) synoptic protocol for the pathological evaluation of penile carcinoma specimens. Link: https://documents.cap.org/protocols/cp-penis-17protocol-4010.pdf

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for primary tumour

Recommendation
4. Perform a detailed physical examination of the penis and external genitalia, recording morphology, size, and location of the penile lesion, including extent and invasion of penile (adjacent) structures. (Strength rating: Strong)
Assessment
Endorsed

Recommendation
5. Perform magnetic resonance imaging (MRI) of the penis/primary tumour (artificial erection not mandatory) when there is uncertainty regarding corporal invasion and/or the feasibility of (organ-sparing) surgery. If MRI is not available, offer ultrasound (US) as alternative option. (Strength rating: Weak)
Assessment
Endorsed with change
Change
In Ontario, there may be delays in obtaining MRI scans, which is the preferred modality. Ultrasound is an alternative option if timely access to MRI is not possible.

Recommendation
6. Obtain a pre-treatment biopsy of the primary lesion when malignancy is not clinically obvious, or when non-surgical treatment of the primary lesion is planned (e.g., topical agents, laser, radiotherapy). (Strength rating: Strong)
Assessment
Endorsed

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for inguinal lymph nodes (LN)

Recommendation
7. Perform a physical examination of both groins. Record the number, laterality and characteristics of any palpable/suspicious inguinal nodes. (Strength rating: Strong)
Assessment
Endorsed

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for clinically node-negative (cN0)

Recommendation
8. If there are no palpable/suspicious nodes (cN0) at physical examination, offer surgical LN staging to all patients at high risk of having micro-metastatic disease (T1b or higher). (Strength rating: Strong)
Assessment
Endorsed

Recommendation
9. In case of T1a G2 disease, also discuss surveillance as an alternative to surgical staging with patients willing to comply with strict follow-up. (Strength rating: Weak)
Assessment
Endorsed

Recommendation
10. When surgical staging is indicated, offer dynamic sentinel node biopsy (DSNB). If DSNB is not available and referral is not feasible, or if preferred by the patient after being well informed, offer inguinal lymph node dissection (ILND) (open or video-endoscopic). (Strength rating: Strong).
Assessment
Endorsed with change
Change
DSNB availability is limited in Ontario.

Recommendation
11. If DSNB is planned, perform inguinal US first, with fine needle aspiration cytology (FNAC) of sonographically abnormal LNs. (Strength rating: Strong)
Assessment
Endorsed

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for clinically node-positive (cN+)

Recommendation
12. If there is a palpable/suspicious node at physical examination (cN+), obtain (image-guided) biopsy to confirm nodal metastasis before initiating treatment. (Strength rating: Strong)
Assessment
Endorsed with change
Change
Most patients will not need a biopsy to confirm nodal metastasis (if the node(s) are obviously pathologic or if there is a >=T1b primary). Requiring a biopsy may delay treatment. In cases of clinical uncertainty, a biopsy may be required if it will alter management.
If FNA is available, it is an alternative to image guided biopsy.

Recommendation
13. In cN+ patients, stage the pelvis and exclude distant metastases with 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18FDG-PET) computed tomography (CT) or CT of the chest and abdomen before initiating treatment. (Strength rating: Strong)
Assessment
Endorsed with change
Change
CT of the chest and abdomen should include the pelvis.
PET is only available on a case-by-case basis upon review and approval of a request made through the PET Access program.

Guidelines Section 6.1.5 Recommendations
6. DISEASE MANAGEMENT
6.1.5. Summary of recommendations for local treatment of penile carcinoma

Recommendation
14. Offer a balanced and individualised discussion on benefits and harms of possible treatments options with the goal of shared decision making. (Strength rating: Strong)
Assessment
Endorsed

Recommendation
15. Inform patients of the higher risk of local recurrence when using organ-sparing treatments compared to amputative surgery. (Strength rating: Strong)
Assessment
Endorsed

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for topical therapy

Recommendation
16. Offer topical therapy with 5-fluorouracil or imiquimod to patients with biopsy-confirmed penile intra-epithelial neoplasia (PeIN). (Strength rating: Weak)
Assessment
Endorsed with change
Change
Imiquimod is currently not publicly funded in Ontario but is widely available.

Recommendation
17. Clinically assess treatment effects after a treatment-free interval and in cases of doubt perform a biopsy. If topical treatment fails, it should not be repeated. (Strength rating: Weak)
Assessment
Endorsed

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for laser ablation

Recommendation
18. Offer laser ablation using CO2 or Nd:YAG laser to patients with biopsy-confirmed PeIN, Ta or T1 lesions. (Strength rating: Weak)
Assessment
Endorsed with change
Change
Laser therapy for T1 lesions may be associated with higher recurrence rates and hence should be reserved for select patients.

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for organ-sparing treatment: surgery (circumcision, wide local excision, glansectomy and glans resurfacing)

Recommendation
19. Offer organ-sparing surgery and reconstructive techniques to patients with lesions confined to the glans and prepuce (PeIN, Ta, T1–T2) and who are willing to comply with strict follow-up. (Strength rating: Strong)
Assessment
Endorsed with change

Change
For superficial cancers (PeIN, Ta, T1) on the shaft, organ-sparing surgery may also be used only if feasible to resect with negative margins.

Recommendation
20. Perform intra-operative frozen section analysis of resection margins in cases of doubt on the completeness of resection. (Strength rating: Weak)
Assessment
Endorsed

Recommendation
21. Offer salvage organ-sparing surgery to patients with small recurrences not involving the corpora cavernosa. (Strength rating: Weak)
Assessment
Endorsed

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for organ-sparing treatment: radiotherapy (EBRT and brachytherapy)

Recommendation
22. Offer radiotherapy to selected patients with biopsy-confirmed T1 or T2 lesions. (Strength rating: Strong)
Assessment
Endorsed

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for amputative surgery (partial- and total penectomy)

Recommendation
23. Offer partial penectomy, with or without reconstruction, to patients with invasion of the corpora cavernosa (T3) and those not willing to undergo organ-sparing surgery or not willing to comply with strict follow-up. (Strength rating: Strong)
Assessment
Endorsed

Recommendation
24. Offer total penectomy with perineal urethrostomy to patients with large invasive tumours not amenable to partial amputation. (Strength rating: Strong)
Assessment
Endorsed

Recommendation
25. Offer amputative surgery to patients with large local recurrences or corpora cavernosa involvement. (Strength rating: Weak)
Assessment
Endorsed

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for multimodal therapy

Recommendation
26. Offer induction chemotherapy followed by surgery to responders, or chemo-radiotherapy to patients with non-resectable advanced primary lesions, or to patients with locally advanced-disease who refuse surgical management. (Strength rating: Weak)
Assessment
Endorsed

Guidelines Section 6.2.2.6 Recommendations
6.2.2.6. Summary of recommendations for radical inguinal lymph node dissection in cN1-2 disease

Recommendation
27. In patients with cN1 disease offer either ipsilateral:
a. fascial-sparing inguinal lymph node dissection (ILND)
b. open radical ILND; sparing the saphenous vein, if possible. (Strength rating: Strong)
Assessment
Endorsed with change
Change
Some variation exists in the surgical approach to cN1 disease, specifically whether fascia should be spared or not. See chapter 6.2.2.6. of the EAU-ASCO guideline, "Summary of recommendations for radical inguinal lymph node dissection in cN1-2 disease". Link: https://uroweb.org/guidelines/penile-cancer/chapter/disease-management.

Recommendation
28. In patients with cN2 disease offer ipsilateral open radical ILND; sparing the saphenous vein, if possible. (Strength rating: Strong)
Assessment
Endorsed with change
Change
In Ontario, both neoadjuvant chemotherapy and surgery are treatment options in patients with cN2 nodal disease. It is recommended to discuss both treatment options with the patient.

Recommendation
29. Offer minimally-invasive ILND to patients with cN1–2 disease only as part of a clinical trial. (Strength rating: Strong)

Assessment
Endorsed

Recommendation
30. Offer neoadjuvant chemotherapy as an alternative approach to upfront surgery to selected patients with bulky mobile inguinal nodes or bilateral disease (cN2) who are candidates for cisplatin and taxane-based chemotherapy (see Section 6.4.1). (Strength rating: Weak)
Assessment
Endorsed with change
Change
In Ontario, both neoadjuvant chemotherapy and surgery are treatment options in patients with cN2 nodal disease. It is recommended to discuss both treatment options with the patient.

Recommendation
31. Complete surgical inguinal and pelvic nodal management within three months of diagnosis (unless the patient has undergone prior neoadjuvant chemotherapy). (Strength rating: Weak)
Assessment
Endorsed

Guidelines Section 6.2.3.6 Recommendations
6.2.3.6. Summary of recommendations for prophylactic pelvic lymph node dissection

Recommendation
32. Offer open or minimally-invasive prophylactic ipsilateral pelvic lymphadenectomy to patients if:
a. three or more inguinal nodes are involved on one side on pathological examination
b. extranodal extension is reported on pathological examination. (Strength rating: Weak)
Assessment
Endorsed with change
Change
May offer radiotherapy with or without chemotherapy as an alternative.

Recommendation
33. Complete surgical inguinal and pelvic nodal management within three months of diagnosis (unless the patient has undergone neoadjuvant chemotherapy). (Strength rating: Weak)
Assessment
Endorsed

Guidelines Section 6.3.5 Recommendations
6.3.5. Summary of recommendations for the surgical management of cN3 disease

Recommendation
34. Offer neoadjuvant chemotherapy (NAC) using a cisplatin- and taxane-based combination to chemotherapy-fit patients with pelvic lymph node involvement or those with extensive inguinal involvement (cN3), in preference to up front surgery. (see Section 6.4.1). (Strength rating: Weak)
Assessment

Endorsed

Recommendation
35. Offer surgery to patients responding to NAC in whom resection is feasible. (Strength rating: Strong)
Assessment
Endorsed

Recommendation
36. Offer surgery to patients who have not progressed during NAC, but resection is feasible. See also (chemo)radiation. (Strength rating: Weak)
Assessment
Endorsed

Recommendation
37. Do not offer Video Endoscopic Inguinal lymphadenectomy. (Strength rating: Strong)
Assessment
Endorsed

Guidelines Section 6.4.1.3 Recommendations
6.4.1.3. Summary of recommendations for neoadjuvant and adjuvant chemotherapy

Recommendation
38. Offer neoadjuvant chemotherapy using a cisplatin- and taxane-based combination to chemotherapy-fit patients with pelvic lymph node involvement or those with extensive inguinal involvement (cN3), in preference to up front surgery. (Strength rating: Weak)
Assessment
Endorsed

Recommendation
39. Offer chemotherapy as an alternative approach to upfront surgery to selected patients with bulky mobile inguinal nodes or bilateral disease (cN2) who are candidates for cisplatin and taxane-based chemotherapy. (Strength rating: Weak)
Assessment
Endorsed with change
Change
Change: In Ontario, both neoadjuvant chemotherapy and surgery are treatment options in patients with cN2 nodal disease. It is recommended to discuss both treatment options with the patient.Endorsed with change

Recommendation
40. Have a balanced discussion of risks and benefits of adjuvant chemotherapy with high-risk patients with surgically resected disease, in particular with those with pathological pelvic LN involvement (pN3). See also section on post-operative radiotherapy. (Strength rating: Weak)
Assessment
Endorsed

Guidelines Section 6.4.2.3 Recommendations
6.4.2.3. Summary of recommendations for pre- and post-operative radiotherapy

Recommendation
41. Offer adjuvant radiotherapy (with or without chemo sensitisation) to patients with pN2/N3 disease, including those who received prior neoadjuvant chemotherapy. (Strength rating: Weak)
Assessment
Endorsed

Recommendation
42. Offer definitive radiotherapy (with or without chemo sensitisation) to patients unwilling or unable to undergo surgery. (Strength rating: Weak)
Assessment
Endorsed

Recommendation
43. Offer radiotherapy (with or without chemo sensitisation) to cN3 patients who are not candidates for multi-agent chemotherapy. (Strength rating: Weak)
Assessment
Endorsed

Guidelines Section 6.5.4 Recommendations
6.5.4. Summary of evidence and guidelines for systemic and palliative therapies for advanced penile cancer
Recommendation(s) for Systemic therapies

Recommendation
44. Offer patients with distant metastatic disease, platinum-based chemotherapy as the preferred approach to first-line palliative systemic therapy. (Strength rating: Weak)
Assessment
Endorsed

Recommendation
45. Do not offer bleomycin because of the pulmonary toxicity risk. (Strength rating: Strong)
Assessment
Endorsed

Recommendation
46. Offer patients with progressive disease under platinum chemotherapy the opportunity to enroll in clinical trials, including experimental therapies within phase I or basket trials. (Strength rating: Strong)
Assessment
Endorsed

Guidelines Section 6.5.4 Recommendations
6.5.4. Summary of evidence and guidelines for systemic and palliative therapies for advanced penile cancer
Recommendation(s) for radiotherapy

Recommendation
47. Offer radiotherapy for symptom control (palliation) in advanced disease. (Strength rating: Strong)
Assessment
Endorsed

Guidelines Section 7.5 Recommendations
7. FOLLOW-UP
7.5. Summary of evidence and guidelines for follow-up and quality of life

Recommendation
48. Deliver penile cancer care as part of an extended multi-disciplinary team comprising of urologists specialising in penile cancer, specialist nurses, pathologists, uro-radiologists, nuclear medicine specialists, medical and radiation oncologists, lymphoedema therapists, psychologists, counsellors, palliative care teams for early symptom control, reconstructive surgeons, vascular surgeons, sex therapists. (Strength rating: Strong)
Assessment
Endorsed with change
Change
In Ontario, cross-sectional radiologists would be a part of the multidisciplinary team.
Consider the following additional resources for palliative and end-of-life care. Link: https://www.cancercareontario.ca/en/cancer-treatments/palliative-care.

Recommendation
49. Follow-up men after penile cancer treatment, initially 3-monthly for two years then less frequently to assess for recurrent disease and to offer patient support services through the extended multi-disciplinary team. At discharge, recommend self-examination with easy access back to the clinic as local recurrence can occur late. (Strength rating: Strong)
Assessment
Endorsed with change
Change
Consider stage-based follow-up.

Recommendation
50. Discuss the psychological impact of penile cancer and its treatments with the patient and offer psychological support and counselling services. (Strength rating: Strong)
Assessment
Endorsed

Recommendation
51. Discuss the negative impact of treatments for the primary tumour on penile appearance, sensation, urinary and sexual function so that the patient is better prepared for the challenges he may face. (Strength rating: Strong)
Assessment
Endorsed

Recommendation
52. Discuss the potential impact of lymphoedema as a consequence of inguinal and pelvic lymph node treatment with the patient and assess patients for it at follow-up and refer to lymphoedema therapists early. (Strength rating: Strong)
Assessment
Endorsed

Section 2: Endorsement Methods Overview

This section will include only the Guideline recommendations with suggested changes.

BACKGROUND FOR GUIDELINE

Penile cancer is a rare malignancy characterized by the uncontrolled growth of cells in the tissues of the penis. The incidence of penile cancer in Ontario is relatively low, accounting for approximately 0.2% percent of all cancer cases [2,4]. Risk factors include advancing age, tobacco use, obesity, chronic penile inflammation, UVA phototherapy, low socio-economic status, and certain sexually transmitted infections, specifically HPV [2,5]. The 5-year survival rate for penile cancer in Ontario is 65% [3].

There are currently no Ontario-specific guidelines in this area. The Endorsement of the EAU-ASCO Guidelines on Penile Cancer will address variation in penile cancer care across Ontario. This Endorsed Guideline will improve the quality of patient care by providing an evidence-based approach for healthcare providers to follow.

The purpose of this endorsement document is to provide clinicians with evidence-based recommendations on the diagnosis and treatment of penile cancer.

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was completed by the Penile Cancer Guidelines Development Group (GDG), which includes all members of the Working Group and the Expert Panel (Appendix 1), which was convened at the request of The Cancer Care Integration & Disease Advisory Program (CI-DAP) at Ontario Health (Cancer Care Ontario) (OH (CCO)). The Working Group was responsible for reviewing the evidence and recommendations in the 2023 EAU-ASCO Guidelines on Penile Cancer in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and responding to comments received during the document review process. The Working Group members had expertise in medical oncology, surgical oncology, radiation oncology, and pathology. The External Expert Panel were responsible for the review and approval of the draft endorsement document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1 and were managed in accordance with the OH (CCO) Conflict of Interest Policy.

ENDORSEMENT METHODS

CI-DAP endorses guidelines using the process outlined in OH (CCO)'s Guideline Endorsement Protocol [6]. This process includes selection of a guideline, assessment of the recommendations (if applicable), drafting the endorsement document by the Working Group, internal review by content and methodology experts, and external review by expert Ontario clinicians and other stakeholders.

Ontario Health assesses the quality of guidelines using the AGREE II tool [7]. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in clinical guidelines (Appendix 2).

SELECTION OF GUIDELINES

As a first step in developing this document, a review of candidate guidelines for this Endorsement was completed. With the quality of guidelines produced by the EAU and ASCO, as well as the release of an updated guideline on penile cancer in March 2023, this guideline was deemed to be best suited for review for clinical relevancy.

ASSESSMENT OF GUIDELINE(S)

The GDG chair discussed the guideline options during the Winter 2023 Genitourinary Cancer Advisory Committee (CAC) meeting for consensus on which guideline would be appropriate. The GDG chair and the CAC agreed that the 2023 EAU-ASCO Guidelines on Penile Cancer, as it provides evidence-based recommendations for the diagnosis and treatment of penile cancer [1].

Details of the AGREE II assessment can be found in Appendix 2. The overall quality of the guideline was rated a 6 on a scale from 1 to 7 by appraisers. Appraisers recommended this guideline for use. The AGREE II average quality ratings for the individual domains were varied; scope and purpose received a score of 72.2 %, stakeholder involvement received a score of 75.0%, rigor of development received a score of 69.8%, clarity of presentation received a score of 91.7%, applicability received a score of 52.1%, and editorial independence received a score of 91.7%.

DESCRIPTION OF ENDORSED GUIDELINE

The 2023 EAU-ASCO Guidelines on Penile Cancer provides recommendations on the diagnosis and treatment of patients with penile cancer. The EAU Penile Cancer Guidelines were published in 2000; however, this publication is a complete revision and a joint release by the European Association of Urology and the American Society of Clinical Oncology. The next update to these guidelines is scheduled for 2025.

For the EAU-ASCO guidelines search strategy, the following databases were queried for English publications: EMBASE from 1974-March 2021, Medline from 1946 to present, and the Cochrane Libraries from 1946 to present [1]. Evidence was selected and reviewed by a multidisciplinary group of clinicians, including urologists, pathologists, oncologists, radiation oncologists, and patient advocates. Additional details about the development and update of guidelines can be found at https://uroweb.org/guidelines/penile-cancer/chapter/methods.

ENDORSEMENT PROCESS

The Working Group reviewed each recommendation from the 2023 EAU-ASCO Guidelines on Penile Cancer to determine whether it could be endorsed, endorsed with change(s), or rejected. This determination was based on the agreement of the Working Group with the interpretation of the available evidence presented in the guideline, whether the recommendation was applicable and acceptable to the Ontario context, whether it was feasible for implementation, and whether new evidence had been reported since the guideline was developed that might change any of the recommendations.

For each recommendation, the Working Group considered the following issues:

1) Does the Working Group agree with the interpretation of the evidence and the justification of the original recommendation?
2) Are modifications required to align with the Ontario context?
3) Is it likely there is new, unidentified evidence that would call into question the recommendation?
4) Would additional statements of qualification/clarification be valuable in Ontario?

ENDORSEMENT REVIEW AND MODIFICATIONS

This section only includes recommendations with changes made based on the consensus from the GDG. 36 of the 52 recommendations were endorsed without changes. 16 of the 52 recommendations were endorsed with changes, as listed in the Section 2 Recommendations below (see the Section 1 Recommendations for a list of all 52 recommendations).

Section 2 Recommendations: EAU-ASCO Guidelines (Guidelines) on Penile Cancer recommendations [1]

Guidelines Section 3.4.7 Recommendations
3. EPIDEMIOLOGY AETIOLOGY AND PATHOLOGY
3.4.7. Summary of recommendations for pathological assessment of tumour specimens

Recommendation
2. The pathological evaluation of penile carcinoma specimens must include an assessment of p16 by immunohistochemistry. (Strength rating: Strong)
Assessment
Endorsed with change
Change
May also consider molecular HPV testing, if available.

Recommendation
3. The pathological evaluation of penile carcinoma specimens should follow the ICCR dataset synoptic report. (Strength rating: Strong)
Assessment
Endorsed with change
Change
Ontario has implemented the College of American Pathologists (CAP) synoptic protocol for the pathological evaluation of penile carcinoma specimens. Link: https://documents.cap.org/protocols/cp-penis-17protocol-4010.pdf

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for primary tumour

Recommendation
5. Perform magnetic resonance imaging (MRI) of the penis/primary tumour (artificial erection not mandatory) when there is uncertainty regarding corporal invasion and/or the feasibility of (organ-sparing) surgery. If MRI is not available, offer ultrasound (US) as alternative option. (Strength rating: Weak)
Assessment
Endorsed with change
Change
In Ontario, there may be delays in obtaining MRI scans, which is the preferred modality. Ultrasound is an alternative option if timely access to MRI is not possible.

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for clinically node-negative (cN0)

Recommendation
10. When surgical staging is indicated, offer dynamic sentinel node biopsy (DSNB). If DSNB is not available and referral is not feasible, or if preferred by the patient after being well informed, offer inguinal lymph node dissection (ILND) (open or video-endoscopic). (Strength rating: Strong).
Assessment
Endorsed with change
Change
DSNB availability is limited in Ontario.

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for clinically node-positive (cN+)

Recommendation
12. If there is a palpable/suspicious node at physical examination (cN+), obtain (image-guided) biopsy to confirm nodal metastasis before initiating treatment. (Strength rating: Strong)
Assessment
Endorsed with change
Change
Most patients will not need a biopsy to confirm nodal metastasis (if the node(s) are obviously pathologic or if there is a >=T1b primary). Requiring a biopsy may delay treatment. In cases of clinical uncertainty, a biopsy may be required if it will alter management.
If FNA is available, it is an alternative to image guided biopsy.

Recommendation
13. In cN+ patients, stage the pelvis and exclude distant metastases with 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18FDG-PET) computed tomography (CT) or CT of the chest and abdomen before initiating treatment. (Strength rating: Strong)
Assessment
Endorsed with change
Change
CT of the chest and abdomen should include the pelvis.
PET is only available on a case-by-case basis upon review and approval of a request made through the PET Access program.

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for topical therapy

Recommendation
16. Offer topical therapy with 5-fluorouracil or imiquimod to patients with biopsy-confirmed penile intra-epithelial neoplasia (PeIN). (Strength rating: Weak)

Assessment
Endorsed with change
Change
Imiquimod is currently not publicly funded in Ontario but is widely available.

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for laser ablation

Recommendation
18. Offer laser ablation using CO2 or Nd:YAG laser to patients with biopsy-confirmed PeIN, Ta or T1 lesions. (Strength rating: Weak)
Assessment
Endorsed with change
Change
Laser therapy for T1 lesions may be associated with higher recurrence rates and hence should be reserved for select patients.

Guidelines Section 5.3 Recommendations
5. DIAGNOSTIC EVALUATION AND STAGING
5.3. Summary of recommendations for diagnosis and staging of penile cancer
Recommendation(s) for organ-sparing treatment: surgery (circumcision, wide local excision, glansectomy and glans resurfacing)

Recommendation
19. Offer organ-sparing surgery and reconstructive techniques to patients with lesions confined to the glans and prepuce (PeIN, Ta, T1–T2) and who are willing to comply with strict follow-up. (Strength rating: Strong)
Assessment
Endorsed with change
Change
For superficial cancers (PeIN, Ta, T1) on the shaft, organ-sparing surgery may also be used only if feasible to resect with negative margins.

Guidelines Section 6.2.2.6 Recommendations
6.2.2.6. Summary of recommendations for radical inguinal lymph node dissection in cN1-2 disease

Recommendation
27. In patients with cN1 disease offer either ipsilateral:
a. fascial-sparing inguinal lymph node dissection (ILND)
b. open radical ILND; sparing the saphenous vein, if possible. (Strength rating: Strong)
Assessment
Endorsed with change

Change
Some variation exists in the surgical approach to cN1 disease, specifically whether fascia should be spared or not. See chapter 6.2.2.6. of the EAU-ASCO guideline, "Summary of recommendations for radical inguinal lymph node dissection in cN1-2 disease". Link: https://uroweb.org/guidelines/penile-cancer/chapter/disease-management.

Recommendation
28. In patients with cN2 disease offer ipsilateral open radical ILND; sparing the saphenous vein, if possible. (Strength rating: Strong)
Assessment
Endorsed with change
Change
In Ontario, both neoadjuvant chemotherapy and surgery are treatment options in patients with cN2 nodal disease. It is recommended to discuss both treatment options with the patient.

Recommendation
30. Offer neoadjuvant chemotherapy as an alternative approach to upfront surgery to selected patients with bulky mobile inguinal nodes or bilateral disease (cN2) who are candidates for cisplatin and taxane-based chemotherapy (see Section 6.4.1). (Strength rating: Weak)
Assessment
Endorsed with change
Change
In Ontario, both neoadjuvant chemotherapy and surgery are treatment options in patients with cN2 nodal disease. It is recommended to discuss both treatment options with the patient.

Guidelines Section 6.2.3.6 Recommendations
6.2.3.6. Summary of recommendations for prophylactic pelvic lymph node dissection

Recommendation
32. Offer open or minimally-invasive prophylactic ipsilateral pelvic lymphadenectomy to patients if:
a. three or more inguinal nodes are involved on one side on pathological examination
b. extranodal extension is reported on pathological examination. (Strength rating: Weak)
Assessment
Endorsed with change
Change
May offer radiotherapy with or without chemotherapy as an alternative.

Guidelines Section 6.4.1.3 Recommendations
6.4.1.3. Summary of recommendations for neoadjuvant and adjuvant chemotherapy

Recommendation
39. Offer chemotherapy as an alternative approach to upfront surgery to selected patients with bulky mobile inguinal nodes or bilateral disease (cN2) who are candidates for cisplatin and taxane-based chemotherapy. (Strength rating: Weak)

Assessment
Endorsed with change
Change
Change: In Ontario, both neoadjuvant chemotherapy and surgery are treatment options in patients with cN2 nodal disease. It is recommended to discuss both treatment options with the patient.Endorsed with change

Guidelines Section 7.5 Recommendations
7. FOLLOW-UP
7.5. Summary of evidence and guidelines for follow-up and quality of life

Recommendation
48. Deliver penile cancer care as part of an extended multi-disciplinary team comprising of urologists specialising in penile cancer, specialist nurses, pathologists, uro-radiologists, nuclear medicine specialists, medical and radiation oncologists, lymphoedema therapists, psychologists, counsellors, palliative care teams for early symptom control, reconstructive surgeons, vascular surgeons, sex therapists. (Strength rating: Strong)
Assessment
Endorsed with change
Change
In Ontario, cross-sectional radiologists would be a part of the multidisciplinary team.
Consider the following additional resources for palliative and end-of-life care. Link: https://www.cancercareontario.ca/en/cancer-treatments/palliative-care.

Recommendation
49. Follow-up men after penile cancer treatment, initially 3-monthly for two years then less frequently to assess for recurrent disease and to offer patient support services through the extended multi-disciplinary team. At discharge, recommend self-examination with easy access back to the clinic as local recurrence can occur late. (Strength rating: Strong)
Assessment
Endorsed with change
Change
Consider stage-based follow-up.

EXTERNAL EXPERT PANEL REVIEW AND APPROVAL

Feedback on the approved draft endorsement document was obtained from content experts across Canada, representing urology, medical oncology, surgical oncology, radiation oncology, and pathology (Appendix 1).

For the endorsement document to be approved, 75% of the content experts must vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that voted, 75% must approve the document. The Expert Panel may specify that approval is conditional, and that changes to the document are required.

Of the 9 expert panel members, 9 members voted and 0 abstained, for a total of 100% response between May-July 2024. Of those who voted, 9 approved the document (100%). The main changes from the Expert Panel and the Working Group's responses are summarized in Table 3-1.

Table 1: Summary of the Working Group's responses to changes from the External Expert Panel.

Changes	Responses
1. Recommendation 3: In my opinion CAP and ICCR protocols are equally solid and thorough.	Reframed change statement to reflect the most widely adopted checklist in Ontario. Modified to: "For the pathological evaluation of penile carcinoma specimens, Ontario has implemented the College of American Pathologists (CAP) synoptic protocol. Link: https://documents.cap.org/protocols/cp-penis-17protocol-4010.pdf "
2. Recommendation 12: I think it would be helpful to clarify the two instances where biopsy is not needed. If they have a clinically obvious pathologic node or if they have a >=T1b primary (so they would qualify for LND anyway. Could modify the change statement as follows: "Most patients will not need a biopsy to confirm nodal metastasis (if the node(s) are obviously pathologic or if there is a >=T1b primary), which may delay treatment. In cases of clinical uncertainty, a biopsy may be required if it will alter management."	Adjusted wording of the change statement to that suggested by the Expert Panel member. Modified to: "Most patients will not need a biopsy to confirm nodal metastasis (if the node(s) are obviously pathologic or if there is a >=T1b primary), which may delay treatment. In cases of clinical uncertainty, a biopsy may be required if it will alter management."
3. Recommendation 18: I would add that "laser therapy for T1 lesions should only be used in well selected cases" to the change statement.	Adjusted wording of the change statement to reflect this feedback. Modified to: "Laser therapy for T1 lesions may be associated with higher recurrence rates and hence should be reserved for select patients."
4. Recommendation 19: It is possible to do organ sparing surgery for superficial cancers on the shaft. Some are managed with wide local incision. Potential change statement to:	Assessment changed to "Endorse with change" and the following change statement was added:

"For superficial cancers (PeIN, Ta, T1) on the shaft, organ-sparing surgery can also be used as long as feasible to resect with negative margins."	"For superficial cancers (PeIN, Ta, T1) on the shaft, organ-sparing surgery may also be used as long as feasible to resect with negative margins."
5. Recommendations 28, 30, and 39: Disagreement that upfront surgery is preferable to neoadjuvant chemotherapy in patients with cN2 nodal disease. There is no data to support this. In addition, NCCN guidelines recommend chemo in patients with bilateral nodal disease. A change statement should be added to indicate that both are options that need to be discussed with the patient.	Assessment changed to "Endorse with change" and the following change statement was added for each of the three recommendations: "In Ontario, both neoadjuvant chemotherapy and surgery are treatment options in patients with cN2 nodal disease. It is recommended to discuss both treatment options with the patient."
6. Recommendation 49: For follow-up protocol, 3-monthly for two years regardless of stage is not rational.	Assessment changed to "Endorse with change" and the following change statement was added: "Can consider stage-based follow-up."

DISSEMINATION AND IMPLEMENTATION

The endorsement document will be published on the OH (CCO) website. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. The Guideline Endorsement will also be disseminated among relevant OH (CCO) groups including the Guideline Development Group, the Genitourinary Cancers Advisory Committee, and other key stakeholders who care for patients with penile cancer.

UPDATING THE ENDORSEMENT

CI-DAP at OH (CCO) will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for Ontario.

ACKNOWLEDGEMENTS

The Penile Cancer GDG would like to thank the following individuals for their assistance in developing this report:

- The European Association of Urology (EAU) and the American Society of Clinical Oncology (ASCO) for their permission to endorse their collaborative 2023 Guidelines on Penile Cancer.
- Sheila McNair from the Program in Evidence-Based Care (PEBC) for assisting the CI-DAP with the guideline endorsement process.
- EAU-ASCO for collaborating with CI-DAP to facilitate endorsement of the guideline.

CONCLUSION

The final endorsed recommendations contained in Section 1 reflect feedback obtained through internal review and expert panel review, with the document drafted by the GDG Working Group.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Table 1: Members of the Penile Cancer Guideline Development Group: Working Group

Name	Affiliation	Conflict of Interest
Girish Kulkarni Genitourinary Oncologist Ontario Genitourinary Cancers Lead	University Health Network Ontario Health (Cancer Care Ontario), Toronto, ON	Advisory board participation: Bladder Cancer Canada
Di (Maria) Jiang Medical Oncologist	Princess Margaret Cancer Centre, Toronto, ON	Advisory board participation: EMD Serono, Pfizer, McKesson Canada, AstraZeneca, Merck, Janssen Oncology, Novartis AAA. Site PI for trials: AstraZeneca, Point Biopharma. Speaking engagement (all unrestricted): Bayer, EMD Serono Canada, Janssen Oncology, AstraZeneca, Astellas. Research funding: Lead: creation of patient education videos for patients with metastatic prostate cancer (unrestricted): Amgen, Tersera, Astellas.
Luke Lavallee Surgical Oncologist	The Ottawa Hospital, Ottawa, ON	Honoraria: Tolmar, Merck. Advisory Board Participation: Knight, Astellas, Bayer, AAA. Research Grant: Tolmar.
Gerard Morton Radiation Oncologist	Sunnybrook Health Sciences Centre, Toronto, ON	None declared.
Susan Prendeville Pathologist	University Health Network, Toronto, ON	None declared.
Natalie Drake Specialist, CI-DAP	Ontario Health (Cancer Care Ontario), Toronto, ON	None declared.

Table 2: Members of the Penile Cancer Guideline Development Group: Expert Panel

Name	Affiliation	Conflict of Interest
Bimal Bhindi Urologic Oncologist	Southern Alberta Institute of Urology Calgary, AB	Advisory board participation: Bayer, EMD Serono Canada, Merck. Honoraria: Bayer, Merck
Peter Black Surgical Oncologist	Vancouver General Hospital, Vancouver, BC	Advisory board participation: AbbVie, AstraZeneca, Astellas, Bayer, BMS, CG Oncology, Combat, EMD-Serono, Ferring,

		Janssen, Merck, Nonagen, Nanobot, NanOlogy, Pfizer, Photocure, Prokarium, Sumitomo, TerSera, Tolmar, Verity. Speaking engagement: Janssen, TerSera, Bayer, Pfizer. Clinical trials participation: Genentech, Janssen, CG Oncology, Therelase, Pacific Edge, Pfizer. Patent sharing: Veracyte.
Rodney Breau Surgical Oncologist	The Ottawa Hospital, Ottawa, ON	None declared.
Fadi Brimo Pathologist	MUHC Royal Victoria Hospital McGill University Health Centre, Montreal, QC	None declared.
Christina Canil Medical Oncologist	The Ottawa Hospital, Ottawa, ON	Honoraria: Janssen, EMD Serono Advisory board participation: Astellas, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, Merck, Novartis, Pfizer, Seagen. Speaking engagement: Astellas, EMD Serono, Ipsen, Janssen, Seagen. Advocacy group participation: Kidney Cancer Canada (Member of Medical Advisory Board).
Juanita Crook Radiation Oncologist	BC Cancer Agency Sindi Ahluwalia Hawkins Centre, Kelowna, BC	None declared.
Jason Izard Surgical Oncologist	Kingston Health Sciences Centre, Kingston, ON	Honoraria: Astellas, AstraZeneca, Bayer, Janssen, Knight, Merck, TerSera, Tolmar. Advisory board participation: Astellas, Bayer, Janssen, Knight, Merck, TerSera, Tolmar. PI for clinical trial: AstraZeneca, Merck.
Andrea Kokorovic Surgical Oncologist	Dalhousie University, Nova Scotia Health Authority, Halifax, NS	None declared.
Aly-Khan Lalani Medical Oncologist	Juravinski Cancer Center, Hamilton, ON	Honoraria: AstraZeneca, Bayer, Eisai, Ipsen, Janssen, Merck, Pfizer, Novartis. Research grants: BioCanRx, BMS, EMD Serono, Ipsen, Novartis, Roche.
Walid Shahrour Urologist	Thunder Bay Regional Health Sciences Centre, Thunder Bay, ON	Advisory board participation: Knight Therapeutics, TerSera. Speaking engagement: Knight Therapeutics, Boston, AbbVie.

Appendix 2: AGREE II Score Sheet

Domain	Item	Appraiser 1 Ratings[1]	Appraiser 2 Ratings[1]
1) Scope and Purpose	1. The overall objective(s) of the guideline is (are) specifically described.	6	6
	2. The health question(s) covered by the guideline is (are) specifically described.	5	5
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	5	5
Domain score[2] =	(32-6/42-6)*100 = 26/36*100 = 0.722*100 = **72.2%**	Score =	32
2) Stakeholder Involvement	4. The guideline development group includes individuals from all relevant professional groups.	7	7
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	6	7
	6. The target users of the guideline are clearly defined.	3	3
Domain score[2] =	(33-6/42-6)*100 = 27/36*100 = 0.75*100 = **75%**	Score =	33
3) Rigor of Development	7. Systematic methods were used to search for evidence.	6	7
	8. The criteria for selecting the evidence are clearly described.	2	5
	9. The strengths and limitations of the body of evidence are clearly described.	6	6
	10. The methods for formulating the recommendations are clearly described.	3	6
	11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	7	6
	12. There is an explicit link between the recommendations and the supporting evidence.	6	6
	13. The guideline has been externally reviewed by experts prior to its publication.	6	4
	14. A procedure for updating the guideline is provided.	4	3
Domain score[2] =	(83-16/112-16)*100 = 67/96*100 = 0.6979*100 = **69.8%**	Score =	83
4) Clarity of Presentation	15. The recommendations are specific and unambiguous.	7	6
	16. The different options for management of the condition or health issue are clearly presented.	7	6
	17. Key recommendations are easily identifiable.	7	6
Domain score[2] =	(39-6/42-6)*100 = 33/36*100 = 0.9166*100 = **91.7%**	Score =	39
5) Applicability	18. The guideline describes facilitators and barriers to its application.	7	4
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	6	2
	20. The potential resource implications of applying the recommendations have been considered.	3	1
	21. The guideline presents monitoring and/or auditing criteria.	6	4
Domain score[2] =	(33-8/56-8)*100 = 25/48*100 = 0.5208*100 = **52.1%**	Score =	33

6) Editorial Independence	22. The views of the funding body have not influenced the content of the guideline. 23. Competing interests of guideline development group members have been recorded and addressed.	5 7	7 7
Domain score[2] =	(26-4/28-4)*100 = 22/24*100 = 0.9167*100 = **91.7%**	Score =	26
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	6	6
Overall Guideline Assessment	2. I would recommend this guideline for use.	Yes, with modifications	Yes, with modifications

[1]Rated on a scale from 1 to 7

[2]Domain score = (Obtained score – Minimum possible score) / (Maximum possible score – Minimum possible score)