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Management of Advanced Penile Cancer

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Abstract

Penile squamous cell carcinoma (PSCC) is a rare cancer, with approximately 2000 new cases in the United States and 35,000 globally every year. Multiple risk factors are involved in PSCC, but most importantly, the high-risk human papillomavirus infection is thought to be present in approximately 50% of cases. Penile squamous cell carcinoma presents as localized or locally advanced disease. Multiple prognostic markers have been explored over the past 3 decades, but lymph node status remains the strongest predictor of clinical outcomes. Surgical decisions are based on the primary tumor pathologic findings, nodal clinical examination, and imaging results. Most patients with high-risk advanced PSCC benefit from a multimodal treatment approach combining chemotherapy with consolidation surgical treatment. The role of neoadjuvant chemotherapy with radiation therapy has not been well explored in PSCC. Prospective clinical studies, like the International Penile Advanced Cancer Trial, have been launched to provide high-level evidence for multimodal treatment. The International Penile Advanced Cancer Trial is the first randomized clinical trial among patients with PSCC and is currently accruing, with the expectation to generate results in 2023. Unfortunately, most patients with high-risk locally advanced PSCC will have relapsed or refractory cancer after cisplatin-based combination chemotherapy. These patients have dismal outcomes with salvage chemotherapy, highlighting the major unmet need to expand our knowledge of the disease's biology and develop clinical trials that use novel systemic agents. This narrative review synthesizes relevant publications retrieved from PubMed. Our aim is to discuss current approaches in the management of PSCC, summarize ongoing efforts to improve care, and identify future areas for enhancing our understanding of the disease.

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Penile squamous cell carcinoma (PSCC) is a rare cancer with numerous associated risk factors. Multiple prognostic markers have been explored over the past 3 decades. Most patients with high-risk advanced PSCC benefit from a multimodal treatment approach combining chemotherapy with consolidation surgical treatment. This article discusses current approaches in the management of PSCC, summarizes ongoing efforts to improve care, and identifies future areas for enhancing our understanding of the disease.

INCIDENCE AND RISK FACTORS

Penile squamous cell carcinoma (PSCC) accounts for less than 1% of all malignant neoplasms among men in the United States[1] and Europe,[2,3] but it may represent up to 10% of cancers among men in some Asian, African, and South American countries.[4] There is not much strong epidemiological research available for these latter countries. Some researchers have hypothesized that the disparity in incidence rates may be related to the prevalence of neonatal circumcision, the higher rates of human papillomavirus (HPV) infection, and the hygienic infrastructure specific to these countries.[5,6] The total number of new cases in 2018 worldwide has been estimated to be around 35,000.[7] In 2018, there were an estimated 2080 new cases in the United States, with about 410 deaths related to PSCC.[1] Risk factors that have been associated with PSCC include HPV (30% to 50% of patients),[8-10] smoking (3- to 4-times higher risk),[11-14] and phimosis or lack of circumcision (7- to 10-times higher risk).[14,15] The increased risk associated with a lack of circumcision appears to be due to a history of phimosis among uncircumcised men. In fact, a history of phimosis

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increased the risk of PSCC (odds ratio [OR], 11.4) in comparison to the lower risk in uncircumcised men who did not report a history of phimosis (OR, 0.5; 95% CI, 0.1 to 2.5).[15] Lastly, a specific history of penile-related medical conditions appears to be associated with an observed increased risk of development of PSCC, for example, a history of genital warts (OR, 7.6), penile trauma (OR, 3.5), or urethral stricture (OR, 2.0).[14,15]

We conducted an extensive search of the literature in the PubMed database from January 1, 1987, to January 1, 2020 and retrieved peer-reviewed articles and guidelines. We then summarized their findings, presented in the following sections of this narrative review covering the current approaches in the management of PSCC, ongoing efforts to improve care, and future areas of research.

ARTICLE HIGHLIGHTS

- For high-risk patients with penile squamous cell carcinoma (PSCC), a multidisciplinary approach is needed for optimal disease management.
- The International Penile Advanced Cancer Trial is the first randomized clinical trial aimed to provide level I evidence for the first-line treatment of patients with PSCC.
- Our understanding of PSCC's molecular and immune context will help improve treatment strategies in the future.

INITIAL PRESENTATION, DIAGNOSIS, AND STAGING

Penile cancer almost always presents with a skin abnormality or painless palpable lesion on the penis.[16] Inguinal adenopathy is present in around 50% of cases at diagnosis,[17] whereas distant metastases are uncommon at the initial time of diagnosis, with only 1% to 10% of cases having distant metastases at presentation.[17-19] Initial diagnosis requires a biopsy for tissue confirmation and risk stratification. Penile squamous cell carcinoma has a predictable pattern of local and regional metastasis, and lymph node metastasis is the strongest predictor of survival, with disease-specific survival rates for patients with stage pN0, pN1, pN2, and pN3 disease of 96%, 80%, 66%, and 37%, respectively ($P<.001$).[20] The most important primary tumor pathologic prognostic factors are depth of invasion, tumor grade, lymphovascular invasion, and perineural invasion because they predict risk of nodal spread and mortality. Therefore, the next step after the confirmatory biopsy for the primary tumor assessment includes staging the disease based on the clinical examination, imaging, primary tumor pathologic assessment, and a diagnostic surgical lymph node assessment, if warranted. Accurate assessment of regional lymph nodes is crucial for appropriate management because resection of small-volume, pathologically involved regional lymph nodes can be curative whereas patients with larger lymph node involvement typically are thought to benefit more from neoadjuvant chemotherapy followed by surgical consolidation.

Staging System

The TNM Staging System is used for staging PSCC and to define the prognostic staging to guide therapy.[21] The eighth edition of the TNM system has been implemented in the United States since 2018 and outside the United States starting in 2017, with major differences in comparison to the seventh edition.[22] A major difference in the current TNM Staging System compared with the previous version is the presence of perineural invasion, which was added as another factor to separate T1a disease from T1b disease. Another difference is the nodal category of pN1, which is now defined as 2 or fewer unilateral inguinal metastases with no extranodal extension. Additionally, pN2 is now defined as 3 or more unilateral inguinal metastases or bilateral metastases.[21]

Diagnostic Approach to Clinically Node-Negative Disease

Patients with clinically node-negative disease might still receive surgical lymph node evaluation only if they are in the high-risk group based on the presence of any of the following primary tumor pathologic findings: (1) T2 or

greater tumor,[23,24] (2) high-grade tumor,[25,26] or (3) presence of lymphovascular invasion or perineural invasion.[25,27] These findings are the strongest predictors of lymph node metastases. Both dynamic sentinel node biopsy (DSNB) and superficial or modified inguinal lymph node dissection (LND) (using either an open or minimally invasive approach) can be used for surgical staging among patients with high-risk PSCC, whereas patients with low-risk disease can be spared this procedure and be monitored with active surveillance. Further surgical treatment for patients with high-risk disease is guided by the pathologic results from the surgical staging. Active surveillance is recommended for patients without nodal disease as seen via superficial inguinal LND, and complete ipsilateral inguinal LND is recommended for patients with one positive node without extranodal extension, whereas therapeutic ipsilateral inguinal LND and unilateral or bilateral pelvic LND are recommended for patients with 2 or more lymph node metastases or for any lymph node metastasis with extranodal extension.[28]

Diagnostic Approach for Palpable Lymph Nodes

For men with evidence of palpable adenopathy on clinical examination, baseline staging imaging using computed tomography (CT) or positron emission tomography (PET)—CT to evaluate the extent of disease is considered standard care. Fine-needle aspiration (FNA) biopsy for pathologic assessment can help with treatment planning because definitive surgical treatment is recommended for men with positive results on FNA biopsy and no bulky, pelvic, or fixed lymphadenopathy on imaging. Conversely, for men with low-risk disease (pTis, pTa, pT1a) with clinically suspicious adenopathy and negative results on FNA biopsy, we recommend confirmation with an excisional biopsy for definitive evaluation. For men with high-risk disease (T1b or greater) with clinically suspicious adenopathy and negative FNA biopsy results, a superficial or modified inguinal LND with frozen section evaluation of the nodes is preferred. For patients with proven metastases via FNA or node biopsy, additional imaging studies, such as CT and CT-PET, may be of value in predicting adverse nodal features, such as 3 or more positive nodes, extranodal extension, or pelvic metastases. Patients with these risk factors would benefit from neoadjuvant chemotherapy followed by surgical consolidation. This multidisciplinary approach is preferred over surgical treatment alone and will be discussed in detail subsequently.

CT and PET Imaging

Primary penile cancer staging still mainly relies on physical examination. Magnetic resonance imaging (MRI) can be considered to evaluate tumor extent (invasion of the corpora or urethra) for patients with planned organ-sparing surgical treatment in accordance with the current European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines.[29,30] Computed tomography or MRI facilitates the examination of the inguinal region in obese patients or in those who have previously undergone an inguinal surgical procedure, for whom physical examination alone may be unreliable. Otherwise, the addition of CT or MRI does not appear to improve the sensitivity or specificity of lymph node metastasis detection when compared with physical examination for patients with normal findings on inguinal examination, and management recommendations should be based on the primary tumor risk factors.[29,30]

The use of fluorodeoxyglucose (FDG)—labeled PET/CT in patients with cN0 penile cancer has been evaluated in multiple studies, but they have been limited by patient numbers. Scher et al[31] examined 13 patients with cN0 penile cancer, and FDG-PET/CT had a sensitivity per lesion of 94% and 100% specificity. Leijte et al[32] reported their effort in solely cN0 groin tumors, with 5 of 42 patients having evidence of lymph node metastases, and PET/CT identified only 1, resulting in a sensitivity of only 20% with 92% specificity. In 2012, Souillac et al,[33] in a very small subset of patients

with cN0 penile cancer (N=22), found that PET/CT correctly identified 3 of 4 metastases, with a 75% sensitivity and 87.5% specificity. Also in 2012, a meta-analysis by Sadeghi et al[34] included 7 studies, with the pooled sensitivity per groin for FDG-PET/CT in patients with cN0 penile cancer reported as 56.5% (95% CI, 34.5% to 76.8%). Based on this information, FDG-PET/CT is not recommended for routine staging of cN0 tumors, and surgical staging remains a necessity to identify small inguinal lymph node metastases for staging of patients with cN0 tumors with high-risk features.

Patients with clinically palpable lymph nodes and those with high-risk primary tumors should undergo imaging to define the full extent of disease before beginning multimodal disease management. Both CT and MRI techniques are recommended by the NCCN.[30] In addition, FDG-PET/CT is a recommended imaging modality according to the current EAU guidelines.[29] No prospective evaluation has been performed to compare all 3 modalities and identify the best imaging modality for patients with palpable lymph nodes.

TREATMENT OF LOCALLY ADVANCED PSCC

Regional lymph node involvement remains the strongest predictor of survival for patients with PSCC.[20] Patients who present with locally advanced regional PSCC are at an increased risk for disease-related mortality with surgical treatment alone and are best treated using multimodal approaches. The management of patients with suspected clinical lymphadenopathy is usually to first confirm nodal disease and then determine the extent of disease involvement via a clinical examination, imaging, and percutaneous biopsy. An overview of the different treatment modalities, including selection and sequencing of chemotherapy, radiotherapy, and surgical consolidation with inguinal and pelvic LND, is presented in the following sections.

Role of Neoadjuvant Chemotherapy in Locally Advanced PSCC

Patients with bulky, fixed, or bilateral inguinal lymphadenopathy typically will not benefit from up-front surgical treatment alone.[35] Neoadjuvant systemic therapy for these patients is currently recommended as the preferred strategy by the NCCN and the EAU guidelines.[36,37] Neoadjuvant chemotherapy allows for timely delivery of systemic chemotherapy, results in potential volume reduction for enlarged lymphadenopathies, provides prognostic information, and facilitates subsequent surgical consolidation.[38,39] The important factors to consider when selecting a chemotherapy regimen for such an approach include (1) patient tolerance of the chemotherapy regimen, (2) the overall response rates to the chemotherapy regimen, (3) the percentage of patients proceeding with consolidation surgical treatment, and (4) the pathologic complete response (pCR) rates, which are the strongest predictor of survival for patients with locally advanced PSCC. A review of the currently available systemic chemotherapy regimens is summarized in Table 1.[40,41–43,44]

Unfortunately, there are currently no clinical or pathologic factors that can accurately predict a patient's benefit from neoadjuvant chemotherapy.[49–51] The only strong predictor of better survival after neoadjuvant chemotherapy is achievement of a pCR at the time of consolidative surgical treatment.[41] Limited molecular or imaging biomarkers have been evaluated or determined to be useful for early assessment of the benefit of neoadjuvant chemotherapy, and scarce data are available regarding the possible role of [^{18}F]-FDG–PET for assessing interim response to neoadjuvant therapy.[52,53]

Among the largest trials that have established the approach of neoadjuvant chemotherapy followed by surgical treatment as the standard of care is a prospective single-center nonrandomized phase 2 clinical trial by Pagliaro et al.[41] This study's objective was determining the response rate, time to progression (TTP), and overall survival (OS) of patients with bulky adenopathy who were receiving neoadjuvant chemotherapy in the following combination: paclitaxel (175 mg/m^2 administered over 3 hours on day 1), ifosfamide (1200 mg/m^2 on days 1 to 3), and cisplatin (25 mg/m^2 on days 1 to 3

TABLE 1. Summary of Studies of Systemic Therapy in Locally Advanced or Metastatic Relapsed PSCC

Reference, year	Regimen	Study design	No. of evaluable patients	ORR/CPR (%)	Grade 3-4 toxicity	Median PFS/OS (mo)
Gagliano et al,[40] 1989	Cisplatin	Phase 2	26	15/0	NA	2/4.7
Di Lorenzo et al,[45] 2011	Paclitaxel	Phase 2 in 2nd- line salvage	25	20/0	28% Neutropenia	2.75/5.75
Pickering et al,[46] 2018	Vinflunine	Phase 2 1st-line therapy for stage III/IV	26	27/0	−32% Neutropenia −64% Constipation	2.9/8.4
Pagliaro et al,[41] 2010	Paclitaxel, ifosfamide, and cisplatin (TIP)	Phase 2 1st-line therapy in locally advanced only	30	50/10	3.3% Neutropenia	7.1/13.9
Di Lorenzo et al,[42] 2012	5-Fluorouracil + cisplatin	Retrospective 1st-line therapy for stage III/IV	25	32/0	20% Neutropenia	5/8
Nicholson et al,[43] 2013	Docetaxel, cisplatin, and 5-fluorouracil (TPF)	Phase 2 1st-line therapy for stage III/IV	26	38.5/7.7	−46.4% Neutropenia −68% Any grade 3/grade 4	7.1/13.9
Necchi et al,[47] 2018	Dacomitinib	Phase 2 1st-line therapy for stage III/IV	28	32.1/3.5	−10% Rash	4.1/13.7
Huang et al,[48] 2019	Nimotuzumab	Pilot study in 2nd-line advanced disease	6	33/16	NA	4.8/9.2

CPR = complete pathologic response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PSCC = penil squamous cell carcinoma.

every 3 weeks) (TIP), with the goal of completing a total of 4 cycles before proceeding with consolidation surgical treatment. Thirty men received chemotherapy, and 23 patients (76.7%) completed the planned 4 courses of chemotherapy. The other 7 patients discontinued chemotherapy after 1 to 3 courses; the reasons were rapid tumor progression (3 patients), hypersensitivity to paclitaxel (1 patient), cardiac event (1 patient), and patient's decision not to receive further treatment (2 patients). The study reported that 15 patients (50.0%) had an objective response, with 3 complete responses and 12 partial responses, and 22 patients (73.3%) subsequently underwent consolidation surgical treatment via bilateral inguinal LNDs and unilateral or bilateral pelvic LNDs. Three patients (10%) had a pCR, 9 patients (30.0%) remained alive and free of recurrence at the time of last follow-up (median follow-up, 34 months; range, 14 to 59 months), and 2 patients died of other causes without recurrence. The estimated median TTP was 8.1 months (95% CI, 5.4 to 50 months), and median OS was 17.1 months (95% CI, 10.3 to 60 months).[41] It was noted that an improved TTP and OS were significantly associated with a response to chemotherapy ($P<.001$ and $P=.001$, respectively), absence of bilateral residual tumor ($P=.002$ and $P=.017$, respectively), and absence of extranodal extension ($P=.001$ and $P=.004$, respectively) or skin involvement ($P=.009$ and $P=.012$, respectively). Grade 3 infections (16.7% of patients) were the only adverse event experienced by more than one patient during the chemotherapy phase. This was the first prospective study to estimate the outcomes of multimodal therapy for patients with advanced penile carcinoma, and the study established neoadjuvant chemotherapy with TIP followed by consolidation surgical treatment as the preferred treatment option for patients with bulky lymphadenopathy. Nevertheless, this study has major limitations that are inherent to a single-arm Bayesian trial with few patients.

A recent study evaluated registry data from the National Cancer Database. Among 1123 men diagnosed with locally advanced PSCC, 727 patients underwent LND, highlighting the increased use of chemotherapy from 38% of patients in 2004 to 48% in 2014 ($P<.001$).

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Overall, chemotherapy was used in 31% of the 338 patients with N1 disease, 40% of the 450 patients with N2 disease, and 53% of the 335 patients with N3 disease.[54] Even though this study's findings are limited by the multiple major inherent limitations of survey studies that include selection bias and missing information regarding type of chemotherapy and radiation therapy received, the results from multivariate analysis found that receipt of LND (hazard ratio [HR], 0.64; $P<.001$), but not chemotherapy (HR, 1.01; $P=.95$) or radiotherapy (HR, 0.85; $P=.11$), was associated with significantly improved OS.[54] This study should not be used to form any major clinical conclusions on the role of chemotherapy or radiation in patients with advanced penile cancer because of the inherent limitations. Nevertheless, it highlights the importance of LND as an integral part of the management of this disease.

Role of Adjuvant Chemotherapy in Locally Advanced PSCC

Prospective data on adjuvant chemotherapy are very limited; only small retrospective studies have been reported, as well as large retrospective and multicenter case series. Recently, a large multicenter retrospective study assessed 141 patients with advanced pathologic pelvic lymph node involvement and documented a median OS improvement with the use of adjuvant chemotherapy.[55] This study has the inherent limitations of a retrospective study and incomplete information available for the specific chemotherapy combinations used. However, the study does highlight a potential benefit of adjuvant chemotherapy use for patients with pelvic lymphadenopathy who did not receive neoadjuvant chemotherapy. Further prospective evaluation of adjuvant systemic chemotherapy in the management of locally advanced PSCC remains pending to define its exact role and benefit.

The NCCN guidelines recommend using adjuvant chemotherapy if neoadjuvant chemotherapy was not given, with level 2A evidence, for patients with high pathologic risk features (pN2, pN3, or extracapsular extension).[36] The guidelines state that there is no conclusive evidence to support this use. Nevertheless, based on extrapolation from the neoadjuvant chemotherapy evidence, the recommendation is for 4 cycles of TIP adjuvant chemotherapy. As an alternative adjuvant regimen, the guidelines suggest 5-fluorouracil with cisplatin if patients cannot receive ifosfamide.[36] Similarly, there is level 2B evidence for adjuvant chemotherapy if neoadjuvant chemotherapy was not given in the current EAU guidelines, and this should be regarded as a treatment option only for patients with pN2 or pN3 disease after lymphadenectomy.[37] As for patients with pN1 disease, the EAU guidelines recommend adjuvant therapy only in the setting of clinical trials.[37]

Role of Adjuvant Radiation Therapy

Radiotherapy with concurrent chemotherapy has become a standard management strategy for head and neck, vulvar, and anal squamous cancers,[56-58] but its use in the perioperative setting in penile cancer is limited by the small number of available studies.[59] The EAU penile cancer guideline group recently conducted a systematic review of the evidence and concluded that because of the heterogeneous and limited evidence of clinical benefit, a routine recommendation of adjuvant radiotherapy is not yet warranted.[60]

In conclusion, the current standard of care is founded on limited data but remains as neoadjuvant chemotherapy with TIP as the preferred regimen, followed by surgical treatment.[41] The care of patients with locally advanced and metastatic PSCC remains best provided at centers of excellence and under the care of an experienced multidisciplinary team. We encourage all oncologists and urologists to enroll patients in clinical trials when available. Until recently, it was not possible to conduct randomized controlled trials in penile cancer to answer the basic management questions. The design of the International Penile Advanced Cancer Trial (InPACT; ClinicalTrials.gov Identifier: NCT02305654) makes this possible, as described subsequently.[61]

InPACT: The First Randomized Clinical Trial Evaluating the Management of Patients With PSCC

InPACT is a large 400-patient clinical trial that will be conducted in the United

TABLE 2. Summary of Genomic Studies in PSCC

Reference, year	Center/country	Study population/HPV status	Type of molecular testing	Findings
McDaniel et al,[76] 2015	Single-center/United States	43/5 HPV+	Next-generation sequencing	*TP53*: 45% *CDKN2A*: 54% *PIK3CA*: 20%
Ali et al,[70] 2016	Multicenter/United States	20/3 HPV+	Next-generation sequencing	*TP53*: 65% *CDKN2A*: 40% *NOTCH1*: 25% *PIK3CA*: 25%
Feber et al,[73] 2016	Multicenter/United Kingdom	27/5 HPV+	Whole-exome sequencing	*TP53*: 15% *FAT1*: 15% *CSN1S1* (previously *CSN1*): 11%
Marchi et al,[75] 2017	Single-center/Brazil	20/5 HPV+; 30 validation	Genome-wide copy number alteration DNA methylation miRNA and mRNA analysis	Worse OS associated with *BIRC5* and *DNMT3B* Identified 10 top driver candidates
Chahoud et al,[72] 2019	Single-center/United States	34/10 HPV+	Whole-exome sequencing	*TP53*: 35% *CDKN2A*: 23% *NOTCH1*: 35% *PIK3CA*: 21% TMB >10: 21%
Jacob et al,[74] 2019	Multicenter/United States	78/22 HPV+	Next-generation sequencing	*TP53*: 58% *CDKN2A*: 47% *NOTCH1*: 22% TMB >10: 18%

HPV = human papillomavirus; miRNA = microRNA; mRNA = messenger RNA; OS = overall survival; PSCC = penile squamous cell carcinoma; TMB = tumor mutational burden; + = positive.

Kingdom, United States, Columbia, and Canada, and it employs a Bayesian design to randomize treatment of patients with inguinal lymph node metastases from PSCC. The study has 2 independent randomizations to answer 2 main questions. The first question is the role of neoadjuvant therapy before standard surgical treatment; this question is being addressed by randomizing patients to the chemotherapy, chemoradiotherapy, or no neoadjuvant therapy treatment arms. This randomization will answer whether there is any benefit for patients to receive neoadjuvant chemotherapy or chemoradiation. The second question concerns the role of prophylactic pelvic LND following the standard surgical treatment with therapeutic inguinal LND among patients with high pathologic risk factors after receiving chemoradiotherapy.[61]

TREATMENT OF RELAPSED OR REFRACTORY ADVANCED PSCC

Role of Systemic Chemotherapy for Relapsed Metastatic Disease

The preferred chemotherapy regimen for patients with distant metastatic or relapsed PSCC after failure of frontline systemic chemotherapy is not clear. However, outcomes are dismal for patients who present with or have development of visceral metastasis.[62] The most commonly used systemic treatment options that have been evaluated in nonrandomized small phase 2 clinical trials for the first-line and subsequent lines of therapies for the management of metastatic PSCC are summarized in Table 1.[40–43,45–48,63] Clinical trial enrollment is the preferred treatment option for patients with relapsed PSCC because all of

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TABLE 3. Summary of Reported Studies on PD-L1 Expression in PSCC

Reference, year	No. of patients	Tumor PD-L1+ (%)	Antibody	Cutoff
Udager et al,[77] 2016	37	23 (62.2)	Clone 5H1	≥5%
Ottenhof et al,[80] 2017	200	96 (48.0)	Clone E1L3N (cell signaling)	≥1%
Cocks et al,[78] 2017	53	21 (39.6)	Clone E1L3N (cell signaling)	Any extent
Deng et al,[79] 2017	116	62 (53.4)	Clone E1L3N (cell signaling)	≥5%
Davidsson et al,[81] 2019	222	72 (32.1)	Clone E1L3N (cell signaling)	≥1%

PD-L1 = programmed cell death ligand 1; PSCC = penile squamous cell carcinoma; + = positive.

the currently available systemic therapy regimens offer only minimal improvement in clinical outcomes, with a median OS of less than 6 months. When enrollment in clinical trials is not possible, 2- or 3-agent combinations are preferred over single agents for patients with good performance status to improve response rates. The decision is tailored on the basis of the type of chemotherapy received and the clinical response to first-line therapy, performance status, and disease burden. Patients should be aware that the evidence for therapies after platinum-based therapy is very limited, and chemotherapy data are mostly extrapolated using clinical trials in the first-line setting. Best supportive care should be considered for patients with relapsed PSCC who do not have the capacity to be enrolled in clinical trials and cannot tolerate further systemic therapy because of deteriorating performance status or major comorbidities.

For palliative therapy, a single-agent regimen with cisplatin alone has displayed modest activity, with an objective response rate (ORR) of 15% in a trial of 26 patients, with an estimated median OS of only 4.7 months and limited toxicity data available.[40] Conversely, paclitaxel monotherapy has been reported to have an initial response rate of close to 30% with minimal toxicity. Therefore, it may be a possible option to discuss with patients in the palliative setting.[44] Recently, a single-agent phase 2 clinical trial using vinflunine, a third-generation compound with less toxicity than older vinca alkaloids, was reported to meet its primary end point. The reported clinical disease control rate was 45% and the ORR was 27%, comparable to 2 chemotherapy combination regimens tested in other phase 2 trials for patients with PSCC.[46] Patients received vinflunine at 320 mg/m^2 every 3 weeks for 4 cycles, and of the 26 patients, 24 had stage IV disease and 2 had stage IIIB disease. The median progression-free survival was disappointing at 2.9 months, and median OS was 8.4 months. Prespecified adverse events that occurred in at least 10% of patients included constipation (64%, grade 3) and neutropenia (32%, grade 3 or higher).[46] Another phase 2 trial evaluated dacomitinib among 28 patients with treatment-naive PSCC, with an ORR of 32%. We will further discuss this clinical trial in the section regarding targeted therapies.[47] Importantly, all of the previously discussed results are mostly from the frontline setting because a very limited number of trials have been published to date in the second-line treatment setting.

Summary of Molecular Data and Role of Targeted Therapy in PSCC

Multiple studies have established that PSCC primary tumors and metastases highly express epidermal growth factor receptor (EGFR) on immunohistochemistry (IHC), but targetable activation of *EGFR* (for expansion of gene symbols, use search tool at www.genenames.org) alterations are rarely found on molecular testing.[64] Although this high expression level seen using IHC could suggest that targeting EGFR might yield safe and effective therapy, multiple case reports and retrospective series have reported only minimal clinical activity with anti-EGFR agents.[64,65] The HER/PTEN/Akt pathway was explored in PSCC and with available targeted treatment options.[66,67]

TABLE 4. Therapeutic Trials With Immune Checkpoint Blockade or HPV-Directed Therapy for PSCC in the United States

ClinicalTrials.gov Identifier	Phase	No. of patients	Tumor type	Prior treatment required?	Agent	Primary end point
Single-agent immune checkpoint blockade trials						
NCT02837042	II	35	Penile carcinoma only	Yes	Pembrolizumab	ORR
NCT02721732	II	250	Rare tumors	Yes	Pembrolizumab	Nonprogression rate at 27 wk
NCT03391479	II	24	Penile carcinoma only	Yes and/or unfit	Avelumab	ORR
Combination immune checkpoint blockade trials						
NCT02496208	I	135	Rare GU tumors	Yes	Nivolumab plus ipilimumab plus cabozantinib	Phase 2 dosing
NCT03333616	II	60	Rare GU tumors	No	Nivolumab plus ipilimumab	ORR
NCT02834013	II	707	Rare tumors	Yes	Nivolumab plus ipilimumab	ORR
NCT03357757	II	39	Any viral-related cancer	No	Avelumab plus valproic acid	ORR (iRECIST)
NCT03074513	II	160	Rare tumors	Yes	Atezolizumab and bevacizumab	ORR
NCT03439085	II	77	HPV+ cancer	Yes	DNA plasmid-encoding interleukin 12/HPV DNA plasmids therapeutic vaccine INO-3112 and durvalumab	ORR
HPV-directed therapy						
NCT02379520	I	32	HPV+ cancer	Yes and/or unfit	HPV-specific T cells with or without lymphodepletion and nivolumab	No. of patients with DLT
NCT03427411	II	120	HPV+ cancer	No	M7824, a novel bifunctional anti–PD-L1/TGFβ trap fusion protein	ORR
NCT03418480	I	44	HPV+ cancer	No	RNA vaccine	No. of patients with DLT
NCT03912831	I	75	HPV+ cancer	Yes	E7 T-cell receptor T cells (KITE-439)	DLT/ORR

DLT = dose-limiting toxicity; GU = genitourinary; HPV = human papillomavirus; iRECIST = Immune-Related Response Evaluation Criteria in Solid Tumors; ORR = objective response rate; PD-L1 = programmed cell death ligand 1; PSCC = penile squamous cell carcinoma; TGFβ = transforming growth factor β; + = positive.

More recently, dacomitinib was approved for metastatic non–small cell lung cancer with *EGFR* alterations.[68] In fact, a phase 2 study by Necchi et al[47] assessed dacomitinib, a second-generation, pan-HER tyrosine kinase inhibitor, among 28 chemotherapy-naive patients with locally advanced or metastatic PSCC, irrespective of their *EGFR* mutational status. The ORR for dacomitinib was 32.1%, with a median progression-free survival of 4.1 months and OS of 13.7 months. The treatment was well tolerated, with only 10% of patients having development of grade 3 to 4 rash as the major toxicity.[47]

Limited understanding of the molecular drivers involved in PSCC progression has hindered the development of personalized therapy. Targeted therapy has the potential to improve treatment outcomes for patients with relapsed PSCC.[69] Previous profiling efforts have identified recurrent alterations in PSCC, including alterations in *TP53*, *CDKN2A*, *NOTCH1*, and *PIK3CA*.[70-76] These studies, summarized in Table 2, have been limited by sample size, number of HPV-positive cases, and variability in molecular testing methods, but they have most recently identified that more than 40% of patients

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with metastatic PSCC have potential targeted therapy opportunities.[69] These factors included alterations in the mammalian target of rapamycin pathway and DNA repair pathway, which could constitute a potential avenue for targeted therapy to be explored in future clinical trials for patients with relapsed PSCC via polyadenosine diphosphate–ribose polymerase inhibitors or PI3K mammalian target of rapamycin inhibitors.

Rationale for and Role of Immunotherapy and HPV-Directed Therapy for Patients With PSCC

Immune checkpoint blockade is the center of clinical investigation and has changed the treatment landscape in many solid tumors over the past decade.[74] Biomarkers of response to checkpoint inhibitors are an area of active research interest, and multiple small studies have determined that 32% to 62% of PSCC tumor tissues test positive for programmed cell death ligand 1 expression on IHC,[77-81] which has been used in other tumor types as a predictive biomarker for response to immune checkpoint blockade (Table 3). A tumor mutational burden of 10 or more alterations per megabase in lung cancer,[82] seen in as many as 21% of PSCC specimens by our group,[72] may also be a predictive biomarker, but validation of these early attempts remains pending. Therefore, drug development with immune checkpoint blockade to treat patients with PSCC is currently being investigated. Table 4 summarizes ongoing clinical trials with immune checkpoint blockades for patients with advanced PSCC.

From the aforementioned evidence, we can see that (1) there is a lack of immunotherapy trials in the neoadjuvant first-line treatment setting, (2) there is limited availability of trials evaluating immune checkpoint blockade as a single agent or in combination with antiangiogenic agents, and (3) that the majority of trials are tumor-agnostic basket trials. In the era of immunotherapy, investigation of chemotherapy and immunotherapy combinations in the neoadjuvant setting is justified because it has proved to be feasible and safe and has clinical activity in lung cancer.[83] This combination should be the interest of future collaborative groups' clinical trials because it has the potential to improve the current standard of care.

Another research focus should be HPV-directed therapies based on HPV tumor tissue testing for all patients with advanced disease. The HPV proteins E6 and E7 have key roles in HPV-mediated carcinogenesis and in the pathogenesis of PSCC. Thus, there has been an interest in targeting the HPV pathway with adoptive T-cell therapy, selected for E6 and E7 reactivity, and this hypothesis is being tested in HPV-related cancers in combination with programmed cell death ligand 1 inhibition. Approximately 50% of cases of PSCC are related to high-risk HPV infection, and Table 4 includes some of the trials available for US patients with PSCC who have HPV-positive cancers.

CONCLUSION

In summary, the management of locally advanced PSCC warrants a multidisciplinary approach at centers of excellence for high-risk patients. The optimal sequencing of such an approach is currently under evaluation by the first randomized clinical trial for patients with PSCC. The InPACT trial will provide much-needed level 1 evidence for the management of patients with locally advanced PSCC. This trial has several translational objectives, which will also provide future molecular and immunologic profiles to determine mechanisms of progression and chemotherapy resistance in PSCC. Also, this trial will expedite crucial drug development to improve on the current first-line and salvage treatment options for patients with PSCC by setting up multiple centers of excellence and improving accruals to clinical trials among patients with a rare cancer. Patients with relapsed PSCC have poor clinical outcomes with systemic chemotherapy. Collaboration between academic centers of excellence and industry is of utmost importance to design and support clinical trials that aim to improve the survival and quality of life for our patients.

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Abbreviations and Acronyms: **CT** = computed tomography; **EAU** = European Association of Urology; **EGFR** = epidermal growth factor receptor; **FDG** = fluorodeoxyglucose; **FNA** = fine-needle aspiration; **HPV** = human papillomavirus; **HR** = hazard ratio; **IHC** = immunohistochemistry; **InPACT** = International Penile Advanced Cancer Trial; **LND** = lymph node dissection; **MRI** = magnetic resonance imaging; **NCCN** = National Comprehensive Cancer Network; **OR** = odds ratio; **ORR** = objective response rate; **OS** = overall survival; **pCR** = pathologic complete response; **PET** = positron emission tomography; **PSCC** = penile squamous cell carcinoma; **TIP** = paclitaxel, ifosfamide, and cisplatin; **TTP** = time to progression

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