

## Complete remission of locally advanced penile squamous cell carcinoma after multimodality treatment

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### Abstract

Treatment of locally advanced penile squamous cell carcinoma (pSCC) remains highly controversial secondary to disease rarity and lack of prospective randomized controlled trials. The current mainstays of care are multimodality treatment with neoadjuvant chemotherapy and surgery. However, clinicians often have difficulty making recommendations for patients unable to tolerate chemotherapy or surgery due to scarcity of data to guide clinical decision-making. We report two cases of locally advanced pSCC that achieved complete remission after treatment with cisplatin-based neoadjuvant chemotherapy and surgery in one case, and concurrent cisplatin chemoradiation in a second, supporting the use of chemotherapy as part of first-line multimodal therapy. We also discuss additional treatment options for patients unable to tolerate traditional chemotherapy regimens.

### Introduction

Penile squamous cell carcinoma (pSCC) is a rare disease with high morbidity and mortality. It most commonly affects men between 50 and 70 years of age.<sup>1</sup> Penile cancer accounts for 0.4-0.6% of all malignant neoplasms among men in the United States (US) and Europe, but exhibits higher incidence, up to 10%, in some developing countries.<sup>2</sup> In 2016, the American Cancer Society projects 2,030 new cases and 340 deaths from penile cancer in the US.<sup>3</sup>

Penile malignancy most commonly presents in the glans penis as a localized mass, ulcer or inflammatory lesion. However, it can be a

locally aggressive cancer with early nodal involvement followed by systemic dissemination. Prognosis is stratified by pathologic TNM staging, and inguinal and pelvic lymph node involvement has been independently linked to decreased five-year cancer-specific survival.<sup>4</sup> The 5-year overall survival (OS) for pT1-3 without nodal involvement is 50-90% versus 30% for stage 3 disease with mobile unilateral or bilateral inguinal lymph nodes.<sup>4</sup>

The treatment for locally advanced pSCC is controversial secondary to a lack of prospective randomized controlled trials. The National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) both recommend four cycles of a cisplatin (CDDP)-based regimen for neoadjuvant chemotherapy (NAC) in unresectable locally advanced pSCC involving multiple, fixed, or bulky inguinal lymph nodes greater than or equal in size to 4 cm or pelvic lymph nodes.<sup>5,6</sup> For patients who are either not surgical candidates or ineligible for CDDP, concurrent chemoradiotherapy with a non-CDDP radiosensitizing agent may be offered.<sup>5</sup> Both populations can have long-term disease-free survival if a complete remission is achieved, illustrated in this case series.

### Case Report #1

A previously healthy 61-year-old man presented to the hospital with a large fungating mass in his perineum, which he reported began as a penile ulceration and progressed to painless auto-amputation of the penis over the subsequent year. A suprapubic tube was immediately placed to drain the bladder, and the genital lesion was biopsied with pathology showing pSCC. Baseline staging computed tomography (CT) scan demonstrated clinical stage IV (cT4N3M0) disease composed of bilateral, palpable, external iliac and inguinal adenopathy in the setting of a large, heterogeneous, enhancing mass, extending from the base of the penis and scrotum, into the perineum posteriorly to the anus, and superiorly superficial to the rectus abdominis muscle above the level of the pubic symphysis (Figure 1A). He received four cycles of NAC with paclitaxel (PTX) (175 mg/m<sup>2</sup>) on day 1, and CDDP (25 mg/m<sup>2</sup>) and ifosfamide (IFO) (1200 mg/m<sup>2</sup>) (also called TIP) on days 1-3. Restaging CT following completion of NAC demonstrated significant reduction in tumor burden, and flexible sigmoidoscopy confirmed lack of rectal involvement. One month after he finished NAC, he underwent radical total penectomy, total scrotoectomy, bilateral orchiectomy and cystoscopy. Pathology demonstrated a 9.5cm pT3Nx pSCC with moderate differentiation, invasion into the urethra, and negative

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surgical margins. Restaging scans performed three months later showed no evidence of residual or recurrent tumors, decreased size of previously enlarged lymph nodes, and no new lymphadenopathy (Figure 1B). He then underwent staged superficial and deep ilioinguinal lymph node dissection (LND) of the left side followed by the right side two months later. Pathology revealed no evidence of residual malignancy, and non-caseating granuloma was identified in all 9 left nodes and 5 out of 6 right nodes. The patient tolerated his surgical procedures well and had uncomplicated postoperative courses. Two years after the completion of NAC surveillance CT shows no evidence of recurrent or metastatic disease.

### Case Report #2

A 68 year-old male presented with a nine-month history of a right groin mass and induration of the glans penis causing a bifurcated urine stream and obstructive voiding symptoms. He had multiple medical comorbidities including non-ischemic cardiomyopathy [ejection fraction (EF) 20%], chronic atrial fibrillation status post placement of an implantable cardioverter defibrillator and necessitating therapeutic anticoagulation, chronic renal insufficiency (baseline Cr 1.5-

2.0), and history of alcohol dependence. Urethroscopy and cystoscopy could not be performed due to chronic urethral meatus narrowing. Baseline staging CT showed clinical stage IV (cTxN3M0) disease with a 2 cm soft tissue mass at the glans and palpable bilateral inguinal, femoral, and external iliac lymphadenopathy measuring up to 2.1×1.8 cm that was hypermetabolic on position emission tomography (PET) (Figure 2A). Biopsy of the lesion demonstrated well- to moderately-differentiated invasive pSCC. He underwent a partial penectomy for primary tumor resection with negative surgical margins, and pathology demonstrated a 2.5 cm moderately differentiated pT2Nx pSCC of keratinizing type, infiltrating the corpora and extending up to but not invading the urethra. He then received adjuvant chemoradiation with weekly CDDP (35 mg/m<sup>2</sup>) and radiation therapy to the bilateral femoral, inguinal, internal and external common iliac lymph nodes with a total dose of 45 Gy to the uninvolved lymph nodes and 64.8 Gy to the involved lymph nodes. Chemoradiation was complicated by worsened renal function (Cr 2.5-3) and thrombocytopenia necessitating dose-delays of CDDP. PET performed approximately 2 months after completion of chemoradiation demonstrated a complete response to therapy with resolution of hypermetabolic lymphadenopathy (Figure 2B). On surveillance CT 18 months later, he remained free of recurrent or metastatic disease. He continues to have borderline thrombocytopenia, worsened EF (15%), and stable renal function (Cr 3.0).

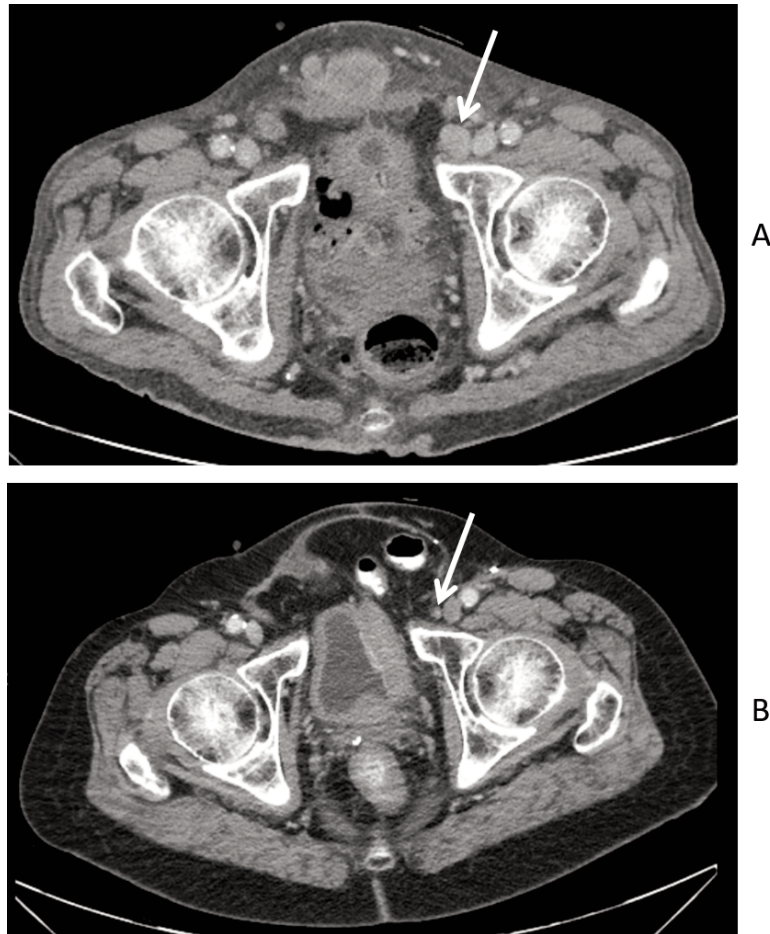


Figure 1. Patient 1, baseline (A) and post-chemotherapy (B) computed tomography abdomen and pelvis.

## Discussion

The single most important prognostic factor in pSCC is lymph node metastasis.<sup>7</sup> Superficial and deep inguinal nodes are usually the first regional nodal groups to manifest lymphatic metastatic spread. Further spread to the pelvic nodes indicates locally advanced pSCC, and any metastasis outside these nodes, is defined as systemic metastatic disease. Pelvic nodal metastases and distant metastases carry a poor prognosis with a median five-year survival rate of 9%.<sup>8</sup> The choice of management in patients with regional lymph node metastases depends on the extent of involvement. For inguinal lymph node metastases (cN1-2), lymphadenectomy with inguinal lymph node dissection is the treatment of choice. For those who have locally advanced disease (cN3), curative-intent multimodal treatment may be offered. In these patients, NAC followed by surgical consolidation has been shown to have a positive effect on survival in those who respond.<sup>9</sup> Neoadjuvant is preferred over adjuvant chemotherapy due to its ability to shrink tumor size, minimize future operations, and

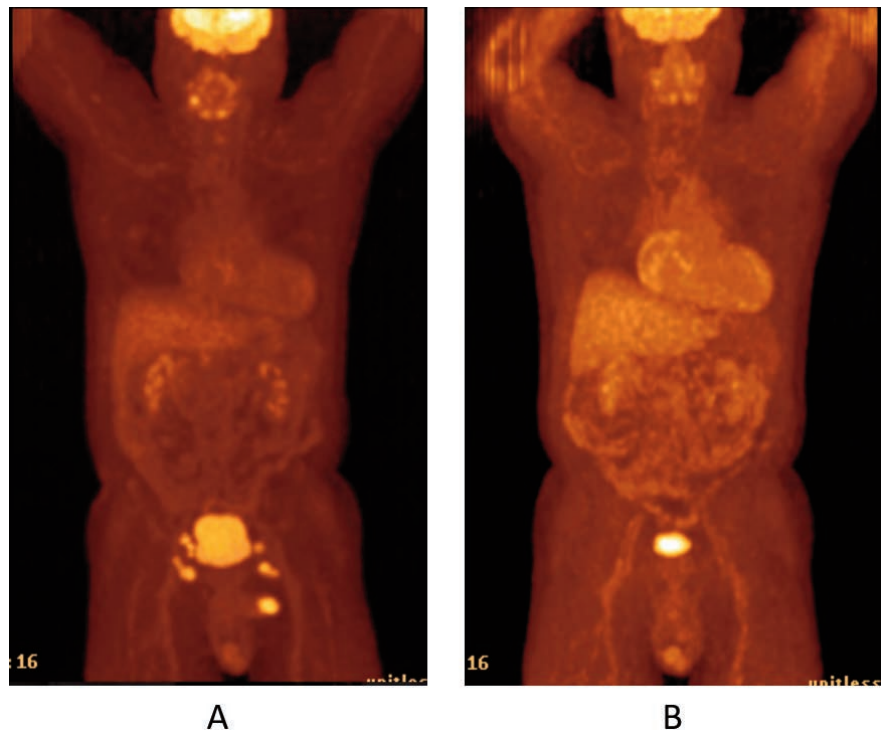


Figure 2. Patient 2, baseline (A) and post-chemoradiation (B) positron emission tomography.

reduce the possibility of micro-metastases.<sup>10</sup> Following completion of treatment, patients should be followed with close radiographic and clinical surveillance for at least five years.

A limited number of studies of NAC for locally advanced penile cancer have been reported in the literature. Rates of complete response (CR) to chemotherapy, defined as total disappearance of lesion on exam and imaging, are generally low. CDDP-based chemotherapy has been shown to achieve higher response rates compared to non-CDDP containing regimens, with a more acceptable toxicity profile and has thus become the mainstream treatment option for patients with advanced pSCC.<sup>11,12</sup> One study evaluated a regimen of bleomycin (Bleo), methotrexate (MTX) and CDDP in 13 patients, with 3 patients (23%) showing signs of disease regression.<sup>13</sup> In another small study reporting three different chemotherapy regimens, 3 patients received Bleo, MTX and CDDP, 5 received IFO, PTX and CDDP, and 2 received PTX and carboplatin. CR was reported in 4 patients (40%) who received IFO, PTX and CDDP, with only partial response (PR) or stable disease (SD) reported in the remaining 6.<sup>14</sup> A study of 20 patients treated with five different regimens using Bleo and/or CDDP with additional agents reported lower rates of CR of 10%.<sup>15</sup> All three studies reported high rates of grade 3 or 4 toxicity due to Bleo, including hematological issues like anemia, leukopenia, thrombocytopenia, and non-hematological problems such as deep vein thrombosis, emboli to lungs and brain, pneumonia and stomatitis.<sup>13-15</sup> One study attributed at least 2 out of 3 toxicity-related deaths to Bleo, and another reported one death from Bleo toxicity.<sup>13,15</sup> A phase II clinical trial using docetaxel (XT), CDDP and fluorouracil (5-FU) reported a response rate of 38.5%, but 65.5% of patients in this study experienced severe or life-threatening toxicities.<sup>16</sup> In the phase II clinical trial by Pagliaro *et al.*, 4 cycles of TIP in patients with N2 or N3 disease without distant metastasis produced clinically significant responses in 50% of patients with 53% experiencing grade 3 or 4 adverse events.<sup>9</sup> The patient in our first case tolerated TIP well and achieved CR with pathology showing only granulomatous tissue post-chemotherapy. Today's aging population is increasingly burdened with cardiac and renal comorbidities, similar to the patient in our second case. For these patients, TIP is unlikely to be tolerated due to known cardiotoxicity with PTX and IFO. In addition, many of these patients are not surgical candidates because of their medical comorbidities. Though CDDP can induce nephropathy in a dose-dependent manner, lower-dose therapy may be tolerated despite preexisting renal dys-

function and is a radiosensitizing agent. Concurrent chemoradiotherapy can potentially increase disease-free survival while avoiding lymph node dissection, though as illustrated by our patient, long-term toxicity such as cytopenias and impaired renal and cardiac function may persist after completion of treatment.

In non-surgical cases or in patients with impaired renal function, we recommend the use of weekly CDDP with doses ranging from 10 mg/m<sup>2</sup> up to 35 mg/m<sup>2</sup> during the course of chemoradiation. In addition, patients should receive education regarding fluid intake and close monitoring of renal function and blood counts throughout treatment. Because CDDP-induced toxicity is mediated by generation of reactive oxygen species, clinical approaches to reduce and prevent these adverse effects with free radical scavenging agents such as amifostine can be considered, though have not gained widespread clinical use.<sup>17</sup>

## Conclusions

For locally advanced pSCC, neoadjuvant therapy with TIP has shown beneficial results with tolerable side effects in a phase II study.<sup>18</sup> For patients with pre-existing end-organ damage or those who cannot tolerate lymphadenectomy, we recommend the use of single-agent CDDP adjusted to pre-existing renal dysfunction with close monitoring of renal function combined with concurrent radiotherapy. Both approaches offer patients the chance to achieve CR and prolonged disease-free survival in select cases.

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