Multimodal Therapy in the Management of Advanced Penile Cancer

Praful Ravi, MBChir, Lance C. Pagliaro, MD

INTRODUCTION

Squamous cell carcinoma (SCC) of the penis is a rare disease, with an estimated 2020 cases and 340 deaths in the United States this year.1 Prognosis is good if disease is diagnosed at a localized stage, but up to 40% of patients present with locally advanced or metastatic disease and outcomes for these patients have historically been poor.2,3 The disease typically spreads in a locoregional manner, first to the draining inguinal lymph nodes, then to pelvic nodes, and then to viscera. The organized nature of spread makes the disease a candidate for a multimodal therapeutic approach, which has been successfully used to treat other SCCs, such as head and neck,4 anus,5 or vulva.6 The rarity of penile cancer in the United States and Western Europe, however, has hampered clinical study into the treatment of locally advanced or metastatic disease and there are currently no randomized data in this setting.

The TNM staging system for penile cancer is shown in Table 1. Advanced disease implies spread beyond the local tissues (ie, T3-4 and/or N1-3 and/or M1 disease); 28% to 64% of men with penile cancer present with clinically palpable inguinal lymph nodes. In such cases, metastatic disease underlies lymphadenopathy in 47% to 85% of such individuals, with the remainder due to inflammatory nodal reaction, and the risk of pelvic nodal metastases is 22% to 56% if the inguinal nodes are involved.7–9 The most important prognostic factor in penile cancer is the presence of inguinal lymph node metastases, with the number of positive lymph nodes, bilateral inguinal nodal disease, pelvic nodal involvement, and extranodal metastatic extension imparting a worse prognosis.10 When inguinal lymphadenopathy is not clinically apparent, micrometastatic disease is present in approximately 25% of cases, with predictive risk factors including tumor stage, grade, and lymphovascular invasion.11

ADJUVANT CHEMOTHERAPY IN NODE-POSITIVE DISEASE

A multimodal approach can be used to treat men who are found node-positive after undergoing...
radical inguinal lymphadenectomy. Although there is evidence to support the use of adjuvant chemotherapy in men with pN2 or pN3 disease, this is based on small numbers of patients and single-center or multicenter retrospective data.

The largest patient series reporting outcomes of adjuvant chemotherapy for penile cancer was recently published and combined data from 4 tertiary centers in the United States, Netherlands, Italy, and China. The investigators identified 84 men who underwent lymph node dissection for SCC of the penis between 1978 and 2013 and who were found to have positive pelvic lymph nodes (ie, pN3). In this cohort, 36 men received adjuvant chemotherapy, with a majority (78%) treated with platinum-based regimens (most commonly docetaxel, cisplatin, and 5-fluorouracil [TPF]), whereas 48 were not. At a median follow-up of just over 12 months, median overall survival was significantly greater in those who had received chemotherapy compared with those who had not (21.7 months vs 10.1 months, \( P = .048 \)) (Fig. 1). Furthermore, receipt of adjuvant chemotherapy (hazard ratio [HR] = 0.40 [0.19–0.87], \( P = .021 \)) was the sole independent predictor of overall survival in a multivariable analysis adjusting for age, pathologic stage, bilaterality of nodal disease, and timing of pelvic surgery.

There are several important limitations of this study, however, the most important being that men who had received salvage chemotherapy after disease recurrence were excluded, which may have led to a systematic bias. The group who had not received adjuvant chemotherapy likely included men who had been unable to receive it owing to rapid postoperative disease recurrence or poor postoperative recovery. In contrast, the group who did receive adjuvant chemotherapy was probably enriched by men who had recovered quickly after surgery (and were thus able to tolerate chemotherapy) and then never recurred, thereby never requiring salvage chemotherapy. In addition to this and potentially other selection biases, the study was inadequately powered for a multivariable analysis.

Other data on the role of adjuvant chemotherapy for pathologic node-positive penile cancer come from smaller, single-center studies. The earliest data on adjuvant treatment came from a pilot study in Milan, Italy, that was published in the late 1980s. Twelve men who had undergone unilateral or bilateral lymphadenectomy for penile cancer, including 5 who had pelvic nodal disease, received weekly vincristine, bleomycin, and methotrexate (VBM) for 12 weeks, with 11 of the 12 patients (92%) alive and disease-free at a median

---

Table 1

TNM staging system for penile cancer

<table>
<thead>
<tr>
<th>T – primary tumor</th>
<th>Tis: Carcinoma in situ</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Tumor invades subepithelial tissue without LVI and is not poorly differentiated/undifferentiated</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invades subepithelial tissue with LVI or is poorly-differentiated/undifferentiated</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades corpus spongiosum and/or cavernosum</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades urethra</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades other adjacent structures</td>
</tr>
<tr>
<td>N – regional lymph nodes</td>
<td>N0: No palpable or visibly enlarged inguinal lymph node</td>
</tr>
<tr>
<td>N1</td>
<td>Palpable mobile unilateral inguinal lymph node</td>
</tr>
<tr>
<td>N2</td>
<td>Palpable mobile multiple unilateral or bilateral inguinal lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral</td>
</tr>
<tr>
<td>M – distant metastasis</td>
<td>M0: No distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1: Distant metastasis</td>
</tr>
<tr>
<td>Pathologic classification</td>
<td>pNX: Cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>pN0: No regional lymph node metastasis</td>
</tr>
<tr>
<td></td>
<td>pN1: Metastasis in a single inguinal lymph node</td>
</tr>
<tr>
<td></td>
<td>pN2: Metastasis in multiple or bilateral inguinal lymph nodes</td>
</tr>
<tr>
<td></td>
<td>pN3: Extraneal extension of lymph node metastasis or pelvic lymph node(s) metastasis</td>
</tr>
</tbody>
</table>

Anatomic staging

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1-3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T1-3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Abbreviation: LVI, lymphovascular invasion.

follow-up of 42 months. There were 2 cases of bleomycin-induced lung injury, however.

Poorer survival outcomes were reported in a small German case series evaluating adjuvant bleomycin, methotrexate, and cisplatin (BMP). Three of 8 men (38%) with pN1-3 disease were alive and free of disease at a mean of 4.5 years after adjuvant treatment, and 1 individual died as a result of lung toxicity secondary to bleomycin. Doublet (rather than triplet) chemotherapy has also been investigated in the adjuvant setting in an effort to reduce toxicity and this approach was shown to achieve good outcomes in a retrospective study from Mumbai, India. A combination of paclitaxel with either carboplatin or cisplatin was used in 19 men with high-risk locally advanced disease (defined as perinodal extension, bilateral nodal involvement, and pelvic node disease and those with incomplete surgical resection) and produced a 2-year overall survival of 68%. At a median follow-up of 15 months, 6 men (32%) had suffered a locoregional relapse, and 3 died (2 due to disease and 1 treatment-related death secondary to diarrhea and neutropenic fever).

The latest data on adjuvant therapy from the Milan group recorded disappointingly poor outcomes in 19 men with pN2 or pN3 disease who received adjuvant cisplatin and 5-FU in combination with a taxane (paclitaxel or docetaxel), termed TPF, with a 2-year disease-free survival of 37%. Additionally, there was substantial hematologic toxicity, with 6 cases of grade 3 or 4 anemia, neutropenia, or thrombocytopenia. These investigators recently evaluated factors associated with better outcomes in men who received adjuvant TPF and found that that p53 immunohistochemical positivity in the nodal metastasis seemed to predict for poorer disease-free survival (HR = 3.76 [0.78–17.96], P = 0.096) and overall survival (HR = 4.29 [0.89–20.57], P = 0.067) in multivariate analyses, although results did not reach statistical significance. These preliminary results are hypothesis generating and merit further study in ongoing efforts to determine which men with advanced penile cancer might benefit most from adjuvant therapy.

**Summary**

Table 2 summarizes the current available evidence on the role of adjuvant chemotherapy in node-positive penile cancer. There are no randomized data, and reported follow-up is short, which raises questions on whether a survival benefit from adjuvant chemotherapy can be durable, while attempts to define predictive and prognostic factors are at a very early stage. Although a majority of patients received a platinum-based regimen,
the optimal combination (doublet or triplet) is also yet to be defined. Nevertheless, taken together, adjuvant platinum-based therapy does have a role in the management of chemotherapy-naïve patients with pelvic node-positive penile cancer, given the premise that it offers the possibility of long-term survival in this cohort of men who might otherwise be expected to relapse without adjuvant treatment.

**MULTIMODAL APPROACH TO BULKY OR UNRESECTABLE NODAL DISEASE**

Surgery alone is rarely a curative option in men with advanced inguinal or pelvic nodal disease. Bilateral, numerous, and bulky inguinal involvement; extranodal extension; and the presence of pelvic nodal metastases are known prognostic factors in penile cancer, and a multimodal approach is desirable in treating patients with these features.\(3,18,19\)

Neoadjuvant chemotherapy offers the ability to downstage disease and thereby enable surgical resection among responders, even among men with advanced penile cancer. Data from the Southwest Oncology Group phase II trial of BMP included examples of bulky inguinal lymph node disease that had a partial response (4 patients) or complete response (2 patients).\(20\) Details of postchemotherapy surgery were not reported in

<table>
<thead>
<tr>
<th>Citation</th>
<th>Patient Cohort</th>
<th>N</th>
<th>Regimen</th>
<th>Median (Mean) Follow-up, mo</th>
<th>Survival Outcomes</th>
<th>Toxicity</th>
</tr>
</thead>
</table>
| Pizzocaro & Piva, \(13\) 1988 | Involved inguinal and/or pelvic nodes | 12 | VBM    | 42                          | • 11 Alive and disease-free  
• 1 Died of disease | Bleomycin-induced lung damage  
(n = 2) |
| Hakenberg et al, \(14\) 2006 | pTx pN1-3 M0 | 8 | BMP    | (54)                        | • 3 Alive and disease-free  
• 4 Died of disease  
• 1 Treatment-related death | Treatment-related death  
(n = 1)  
Any grade 3 or 4  
(n = 24/45) |
| Noronha et al, \(15\) 2012 | High-risk nodal disease (PNE, bilateral nodal disease, pelvic nodal disease, R1 resection) | 19 | TP     | 15                          | • 2-Year OS = 68%  
• 6 Locoregional relapses  
• 2 Died of disease  
• 1 Treatment-related death | Treatment-related death  
(n = 1)  
Any grade 3 or 4  
(n = 6) |
| Nicolai et al, \(16\) 2015 | ≥pN2 M0 | 19 | TPF  (n = 16) Paclitaxel-PF  (n = 3) | N/A              | • 10 Alive and disease-free  
• 8 Died of disease  
• 1 Died of other cause  
• 2-Year DFS of 37% | Any grade 3 or 4  
(n = 10) |
| Sharma et al, \(12\) 2015 | pN3 M0 | 36 | TPF  (n = 18) PF  (n = 8) VBM  (n = 8) TIP  (n = 1) BMP  (n = 1) | 12              | • mOS = 21.7 mo  
(vs 10.1 mo in a cohort of 48 men who did not receive adjuvant chemotherapy),  
\(P = .048\)  
• Adjuvant chemotherapy HR for OS = 0.40  
(0.19–0.87),  
\(P = .021\) | N/A |

**Table 2**

Summary of studies on adjuvant chemotherapy in node-positive penile cancer

*Abbreviations: DFS, disease-free survival; mOS, median overall survival; N/A, not available; PF, cisplatin, 5-FU; PNE, perinodal extension; OS, overall survival; TP, paclitaxel, cis/carboplatin.*
that study, and although a response was seen in nearly 1 in 3 men (including lymph node and distant metastases), toxicity with BMP was significant, with 5 treatment-related deaths (from infection or pulmonary complications) among 45 registered patients. Building on these results, Leijte and colleagues\textsuperscript{21} from the Netherlands reported the outcomes in 20 patients who received neoadjuvant chemotherapy for M0 penile cancer between 1972 and 2005. Although there was heterogeneity in the regimens used (VBM; BMP; 5-FU and cisplatin; cisplatin and irinotecan; and single-agent bleomycin), an overall response (either complete or partial response) was seen in 12 of 19 evaluable patients (63%). Importantly, 8 of the 9 responders who went on to undergo lymphadenectomy had durable long-term survival with no evidence of disease recurrence at a median follow-up of 20 months, with 2 having a pathologic complete response (pCR) on postoperative histology. Response to neoadjuvant therapy was also prognostic, with a 56% 5-year overall survival in men who responded, whereas all nonresponders had died within 9 months of treatment. The similarities between SCC of the penis and head and neck have prompted study of alternative neoadjuvant regimens. The Milan group reported retrospective data on their experience with neoadjuvant TPF, the overall results of which seem slightly poorer compared with the Dutch data. A median of 4 cycles of TPF was administered to 28 men with clinical N3 disease, producing an overall response rate of 43%.\textsuperscript{16} Of the 22 men who subsequently underwent surgery, 7 (32%) were alive and disease-free at a median follow-up of more than 12 months, including 2 of the 4 who achieved a pCR. In the entire cohort, however, 12 men relapsed and 9 died of disease, with an additional 3 deaths due to other causes, including 1 treatment-related death from cardiac toxicity. Response to treatment was also not associated with survival, although the study was underpowered to assess this. These retrospective data served to confirm that neoadjuvant chemotherapy is feasible and potentially effective as part of a multimodal approach against advanced penile cancer. Four prospective studies have added to the evidence base but the small numbers of patients they have accrued make it difficult to generate robust conclusions. The European Organisation for Research and Treatment of Cancer (EORTC) conducted a multi-center phase II study of neoadjuvant irinotecan in combination with cisplatin in 7 men with T3 or N1-2 disease.\textsuperscript{22} A median of 4 cycles of treatment was administered, and 2 men (29%) achieved a clinical response, with a pCR seen in 3 men who underwent postchemotherapy resection. Investigators at the University of Texas MD Anderson Cancer Center conducted the largest prospective study of neoadjuvant chemotherapy for locally advanced disease in the form of a phase II trial enrolling 30 men with clinical stage Tx N2-3 M0 disease, a majority of whom (70%) had clinical N3 disease at baseline.\textsuperscript{23} Patients received 4 cycles of paclitaxel, ifosfamide, and cisplatin (TIP) prior to planned bilateral inguinal and unilateral or bilateral pelvic lymphadenectomy. The treatment was well tolerated, with a majority of men completing all 4 planned cycles and grade 3 infection the most commonly observed adverse event (on 5 occasions). All but 4 individuals went on to undergo lymphadenectomy, including 22 of the 23 men who completed all 4 cycles of chemotherapy. The objective response rate, measured by Response Evaluation Criteria in Solid Tumors (RECIST), was 50% (with 3 complete responses and 12 partial responses) and 3 men had a pCR (13.6%). Survival outcomes were comparable to those seen in retrospective studies,\textsuperscript{16,21} with 9 men (30%) remaining alive and disease-free at a median follow-up of 34 months, with a reported median overall survival within the entire cohort of 17 months. Response to neoadjuvant TIP also predicted for longer time to disease progression and overall survival (Fig. 2). Postoperative complications were comparable to those seen in contemporary lymphadenectomy series,\textsuperscript{24} suggesting that neoadjuvant chemotherapy did not increase surgical morbidity. The same investigators subsequently published a follow-up report by retrospectively reviewing results from an additional 31 men with Tx N1-3 M0 disease who underwent neoadjuvant chemotherapy, predominantly with TIP, to produce an overall cohort of 61 patients.\textsuperscript{25} This report included 21 men who had undergone a prior inguinal procedure and were being treated for disease recurrence or persistence. There was an impressive overall response rate of 65% (39 of 61 men), and the vast majority (85%) went on to undergo surgery, with 10 men (19%) achieving a pCR; 50% of the chemotherapy responders were alive and disease-free at a median follow-up of more than 5 years, as were 7 of the 10 whose surgery had revealed a pCR, suggesting that this multimodal approach to advanced penile cancer had contributed to the observed long-term survival. Prospective studies of other platinum-based regimens in the treatment of metastatic penile cancer have not been as successful as the MD Anderson experience with TIP. A well-designed phase II trial in the United Kingdom involving 21 men with...
Tx N1-3 M0 penile cancer (a majority of whom had N3 disease) aimed to assess response clinically and via RECIST after a planned 3 cycles of TPF and determine how many patients subsequently became operable. The overall response rate was 37% in men with evaluable locally advanced disease, and 5 of 20 patients who were deemed inoperable at trial entry were sufficiently downstaged to proceed with surgery. Toxicity with TPF was substantially greater than that with TIP, however, with more than 2 in 3 patients suffering any grade 3 or 4 adverse events.

The most recent prospective study examining the role of neoadjuvant chemotherapy comes from the Netherlands Cancer Institute and was published in 2015. They used neoadjuvant TPF as part of a nonrandomized institutional study (with a higher dose of cisplatin than that used in the previously described UK TPF phase II trial in 26 men with T4 and/or N3 disease and aimed at downstaging men sufficiently to permit surgery. Almost half of the cohort completed all of the planned 4 cycles, and complete and partial responses (per RECIST) were seen in 2 and 9 patients, respectively, giving an overall response rate of 44% in the 25 evaluable patients. An additional 4 men achieved stable disease, and of the 15 individuals in whom stable disease or better was attained, 14 underwent surgery, with 1 patient having a pCR. Taking into consideration the heterogeneity of the cohort (almost half were treated for recurrent disease, thereby potentially selecting for more aggressive disease biology), survival outcomes were still disappointing. Only 4 men (15%) were alive and disease-free at a median follow-up of 30 months and median overall survival was 10 months, compared with the 17 months seen with TIP. Furthermore, 6 men discontinued therapy owing to toxicity, and all enrolled men experienced at least grade 2 or higher toxicity.

Summary

Table 3 summarizes currently published evidence on the use of neoadjuvant chemotherapy for locally advanced penile cancer. A response rate of 29% to 65% has been seen with the use of neoadjuvant chemotherapy and it is an important part of the multimodal approach to treat advanced penile cancer. The disease seems most sensitive
### Table 3
Summary of studies on neoadjuvant chemotherapy for unresectable nodal disease

<table>
<thead>
<tr>
<th>Citation</th>
<th>Patient Cohort</th>
<th>N</th>
<th>Regimen(s)</th>
<th>Median Follow-up, mo</th>
<th>Response Rate, %</th>
<th>Underwent Surgery (%)</th>
<th>Pathologic Complete Response at Surgery (% of Those Operated)</th>
<th>Survival Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leijte et al, 2007</td>
<td>Tx N0-3 M0</td>
<td>20</td>
<td>BMP (n = 10) VBM (n = 5) Bleomycin (n = 3) PF (n = 1) Cisplatin-irinotecan (n = 1)</td>
<td>23</td>
<td>63</td>
<td>9 (45)</td>
<td>2 (22)</td>
<td>• 5-Y OS = 32% • 8 of 9 undergoing surgery alive and disease-free at median follow-up of 20 mo</td>
</tr>
<tr>
<td>Theodore et al, 2008</td>
<td>T3 N1-2 M0</td>
<td>7</td>
<td>Cisplatin-irinotecan</td>
<td>N/A</td>
<td>29</td>
<td>3 (43)</td>
<td>3 (100)</td>
<td>N/A</td>
</tr>
<tr>
<td>Pagliaro et al, 2010</td>
<td>Tx N2-3 M0</td>
<td>30</td>
<td>TIP</td>
<td>34</td>
<td>50</td>
<td>22 (73)</td>
<td>3 (14)</td>
<td>• 9 Alive and disease-free • mOS = 17 mo</td>
</tr>
<tr>
<td>Dickstein et al, 2016a</td>
<td>Tx N1-3 M0 (including prior inguinal procedure)</td>
<td>61</td>
<td>TIP (n = 53) TP, PF, BMP (n = 7)</td>
<td>N/A</td>
<td>65</td>
<td>52 (85)</td>
<td>10 (19)</td>
<td>• 20 Alive and disease-free at 5 y • 32 Died of disease at 5 y</td>
</tr>
<tr>
<td>Nicolai et al, 2015</td>
<td>Tx N3 M0 (including 5 with relapsed disease)</td>
<td>28</td>
<td>TPF (n = 23) Paclitaxel-PF (n = 5)</td>
<td>N/A</td>
<td>43</td>
<td>22 (79)</td>
<td>4 (18)</td>
<td>• 8 Alive and disease-free • 9 Died of disease • 2-Year DFS = 7%</td>
</tr>
<tr>
<td>Djadjadiningrat et al, 2015</td>
<td>T4 and/or N3 (including 12 with relapsed disease)</td>
<td>26</td>
<td>TPF</td>
<td>30</td>
<td>44</td>
<td>14 (54)</td>
<td>N/A</td>
<td>• 4 Alive and disease-free • 13 Died of disease • mOS = 10 mo • 1-Year OS = 46% • 2-Year OS = 27%</td>
</tr>
</tbody>
</table>

**Abbreviations:** DFS, disease-free survival; mOS, median overall survival; N/A, not available; PF, cisplatin, 5-FU; OS, overall survival; TIP, paclitaxel ifosfamide, cisplatin; TP, paclitaxel, cis/carboplatin.

*a This study included patients from Pagliaro and colleagues, 2010.23*

to platinum-based therapy, with TIP offering the highest response rates. Translating response into a durable survival benefit, however, has proved difficult and optimizing this multimodal approach to do so requires further study. Nevertheless, current European Association of Urology \cite{28} and National Comprehensive Cancer Network \cite{29} guidelines recommend the use, wherever feasible, of a triplet regimen, including cisplatin and a taxane, followed by consolidation surgery in men with bulky or initially unresectable nodal disease who respond to neoadjuvant chemotherapy.

**IS THERE A ROLE FOR CHEMORADIOTherAPY?**

The question of whether chemoradiotherapy may be a feasible option for men with locally advanced and regionally metastatic penile cancer has been raised owing to the superiority of this approach compared with single-modality therapy alone in the treatment of locally advanced SCCs of the vulva and anus, 2 rare perineal tumors that share anatomic and biologic characteristics with penile cancer.\cite{5,6,30} Concurrent chemoradiation has also gained traction because neoadjuvant radiotherapy has been shown to reduce inguinal recurrence rates in men with bulky nodal disease,\cite{31} offering the possibility of synergistic activity with neoadjuvant chemotherapy.

The data on chemoradiotherapy for advanced penile cancer are limited to case reports and case series. The sole multicenter study examining chemoradiation collated data between 2000 and 2012 from 5 tertiary centers in the United States, Canada, and Italy.\cite{32} In this 26-patient cohort, including 16 men with clinical stage IV disease and 5 with M1 disease, a majority received cisplatin-based chemotherapy together with a median dose of 4900 cGy to involved disease areas. Accepting that most patients had stage IV disease at outset and that men with relapsed disease were also included, however, clinical outcomes were disappointing: 1-year overall survival was 37% in men with M0 disease, a figure that is less than that achieved with neoadjuvant chemotherapy alone followed by surgical consolidation.\cite{23}

The extreme paucity of data on chemoradiation for advanced penile cancer are limited to case reports and case series. The sole multicenter study examining chemoradiation collated data between 2000 and 2012 from 5 tertiary centers in the United States, Canada, and Italy.\cite{32} In this 26-patient cohort, including 16 men with clinical stage IV disease and 5 with M1 disease, a majority received cisplatin-based chemotherapy together with a median dose of 4900 cGy to involved disease areas. Accepting that most patients had stage IV disease at outset and that men with relapsed disease were also included, however, clinical outcomes were disappointing: 1-year overall survival was 37% in men with M0 disease, a figure that is less than that achieved with neoadjuvant chemotherapy alone followed by surgical consolidation.\cite{23}

The extreme paucity of data on chemoradiation for advanced penile cancer, therefore, means that this approach is currently investigational, requiring further evaluation within clinical trials, a sentiment that is reflected in consensus guidelines.\cite{28} It is, however, a reasonable treatment option for patients who refuse surgery or are deemed inoperable despite receiving neoadjuvant systemic chemotherapy.

**THE NEED FOR MULTICENTER COLLABORATION**

The rarity of penile cancer means that international and multicenter collaboration is an absolute necessity to enable sufficient accrual of patients into clinical trials such that clinically meaningful results may be produced. The 4 phase II trials of neoadjuvant chemotherapy\cite{22,23,26,27} accrued a combined total of 84 patients across 15 years. The UK study\cite{26} was able to recruit 21 men in just 15 months, which was in part due to the enrollment of patients treated at 9 specialist centers, highlighting the role that collaboration between centers of expertise can play in improving patient recruitment into trials for a rare cancer.

To this end, the UK National Institute for Health Research Cancer Research Network, Cancer Research UK, the US National Cancer Institute, and the EORTC came together in 2011 to form the International Rare Cancers Initiative (IRCI), which aims to facilitate the development of international clinical trials for patients with rare cancers, including penile cancer.\cite{33} The International Penile Advanced Cancer Trial (InPACT; NCT02305654)\cite{34} is the first such IRCI trial for penile cancer and plans to recruit 400 men with locally advanced (ie, nodally metastatic) penile cancer. Men first will be randomized either to standard surgery (inguinal lymphadenectomy), neoadjuvant chemotherapy (with TIP) followed by consolidation surgery, or neoadjuvant chemoradiotherapy (45 Gy in 25 fractions over 5 weeks with weekly cisplatin as a radiosensitizer) followed by surgery. Those who are deemed at high risk of recurrence after inguinal lymphadenectomy will subsequently be randomized to receive either prophylactic pelvic lymphadenectomy or no further surgery. The primary outcome will be overall survival, with secondary outcomes measures, including disease-specific survival, pathologic complete remission rates, quality of life, and surgical complication rates. This trial, which is yet to open, represents a landmark event in the penile cancer field and will provide the first randomized data in the advanced disease setting. It is also hoped that it will open the door to further multiinstitutional collaboration, which is crucial in providing physicians with a robust evidence base on which to base treatment decisions for men with advanced penile cancer.

**SUMMARY**

Although penile cancer remains a rare disease, significant progress has been made in developing an evidence base to support the use of a
multimodal approach to regionally metastatic disease (Fig. 4). Prospective data have shown that neoadjuvant chemotherapy, with TIP seeming the most active regimen followed by surgical consolidation, has the potential to lead to a durable long-term survival, at least in some men. Adjuvant chemotherapy also improves outcomes for men who have undergone lymphadenectomy for resectable disease and who are chemotherapy naïve.

Fig. 4. Summary of current approach to multimodal therapy in men with locoregionally advanced squamous cell penile cancer. +ve, positive; ENE, extranodal extension; ILND, inguinal lymph node dissection; LN, lymph node(s); PLND, pelvic lymph node dissection.

There remain several unanswered questions in the treatment of advanced penile cancer. What factors predict for response to (neo)adjuvant chemotherapy and are prognostic for survival? Is there a role for concurrent chemoradiotherapy? Is it possible to stratify patients by their molecular status or HPV positivity, and how can newer targeted therapies be integrated into the current multimodal treatment paradigm? The answers to these questions will come from international.

Fig. 3. InPACT trial design. ILND, inguinal lymph node dissection; IMRT, intensity-modulated radiotherapy; PLND, pelvic lymph node dissection; RT, radiotherapy.
collaboration across clinical trials, of which the authors hope InPACT to be the first of many.

REFERENCES
