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Current controversies and developments on the role of lymphadenectomy for penile cancer

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Abstract

Penile squamous cell carcinoma is a rare cancer in men. The main prognosticators of survival for penile cancer patients remain the presence and the extent of lymph node metastasis. While radical inguinal lymphadenectomy has been the cornerstone of regional lymph node management for many years, it is still associated with significant morbidity and psychological distress. Recent developments in penile squamous cell carcinoma management have been met with some controversy in the urologic oncology community. Herein, we review the current controversies and developments on the role of inguinal lymphadenectomy for penile cancer.

Keywords: Penile squamous cell carcinoma; Lymph node metastasis; Lymphadenectomy; Minimally invasive surgery; Systemic therapy

Background

Penile cancer (PC) is a rare malignancy in North America and accounts for less than 1% of cancers in men in the United States [1]. Although radical surgery has been the mainstay of primary tumor treatment for many years, this approach can be disfiguring and often leads to significant psychological distress and sexual dysfunction [2]. Surgical treatment of penile squamous cell carcinoma (PSCC) has evolved over time with several innovative penile-sparing approaches becoming increasingly utilized without apparent detrimental impact on oncologic outcomes [3]. While PC has several established prognostic factors, the presence and the extent of regional lymph node (LN) involvement represent the most significant predictors of survival [4,5]. Yet, high level evidence in the management of ilioinguinal nodes remains scarce and the morbidity associated with lymphadenectomy (LAD) generates controversy and results in nonguideline clinical practices.

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Predictors of lymph node metastasis

PC is recognized by a stepwise and orderly nodal spread from the primary tumor to the inguinal nodes followed by the pelvic nodes before progression to systemic disease [4]. Up to 20% of men presenting with nonpalpable nodes harbor occult metastases [6]. Primary tumor grade, stage, histologic subtype, and lymphovascular invasion are the main primary tumor histopathologic features predicting LN involvement [5]. Several authors suggested using biomarkers such as p53, Ki-67, epithelial cadherin, matrix metalloproteinase-9, and squamous cell carcinoma antigen to predict node-positive disease and disease-specific survival, yet none are routinely used for management decisions [7,8]. Only p53 has been successfully incorporated into a predictive nomogram for patients with nonpalpable nodes undergoing LAD [9].

Imaging

Physical examination and imaging are critical in accurate staging of PC patients. In the context of palpable disease, the use of computed tomography (CT) or magnetic resonance imaging (MRI) may be useful in determining the

size, extent, and proximity to surrounding structures. Cross-sectional imaging can also be an adjunct in cases of equivocal or challenging clinical examination (such as with morbid obesity) [10].

The role of CT and MRI is more limited in nonpalpable disease. Small series have shown some promising results with the use of novel imaging modalities such as single photon emission CT and lymphotrophic nanoparticle-enhanced MRI but further studies are required to validate these findings [11,12].

Tumor-node-metastasis (TNM) staging system: Updates in the 8th edition

The latest edition of the American Joint Committee on Cancer Cancer Staging Manual was implemented on January 1st 2018. The changes in the 8th edition of the TNM staging system for penile cancer are summarized in Table 1 [13].

Inguinal lymphadenectomy: Indications, optimal timing and treatment trends

While clinical examination and imaging are limited in evaluating LN involvement, LAD allows for accurate pathologic staging which helps predict outcomes and guide treatment and follow-up strategies. Current guidelines are based on stratification into either low- or intermediate-/high-risk categories according to primary tumor (T) stage [14]. In low-risk cases ($\leq$ pT1a), nonpalpable lymph nodes (cN0) are best managed by surveillance. Recommendations for node-negative (N-) intermediate/high risk cases (pT1b or above) include regional nodal staging with either modified-template inguinal lymph node dissection (ILND) or dynamic sentinel node biopsy (DSNB) in tertiary centers (20 cases/year) [15]. Patients with bulky, bilateral, and/or fixed disease (cN2-3) are best managed with neoadjuvant chemotherapy (NACT) prior to radical LAD (2A). Patients with stable, partial, or complete response following systemic therapy may benefit from surgical consolidation by increasing the potential for disease-free survival [16]. An algorithm of the management of regional nodes in PC patients based on clinical stage is shown in Fig. 1.

No prospective data exists on the optimal timing of ILND and its integration with multimodal therapies in the setting of locally-advanced disease. Although the timing of ILND is controversial, most contemporary series reported superior outcomes for early vs. delayed surgical intervention [17,18]. Typically, ILND is classified as early if performed within 2 to 6 weeks of primary tumor surgery. Whether to perform ILND at the time of penectomy remains unclear, although studies have shown its safety and feasibility [15]. Preoperative antibiotic treatment is no longer recommended [19].

Patients with confirmed pathologic N- disease can expect favorable disease-specific survival [20]. Yet even eradicating micrometastatic disease provides a significant survival benefit rather than waiting for gross nodal disease to occur [17,21,22]. Thus, appropriate surgical management of the ilioinguinal nodes can alter the natural history of node-positive (N+) disease by providing early locoregional control and curing most patients with low-volume disease [17,21].

While it has been reported that prophylactic ILND confers improved long-term survival [23,24], epidemiological studies continue to demonstrate disparities in the receipt of upfront lymphadenectomy for both cN0 and cN+ patients [25,26]. A recent hospital-based analysis revealed an overall rate of LAD of only 27.2% in 2,224 US patients with N-PSCC [27]. The receipt of LAD was associated also with improved overall survival (hazard ratio, 0.79; 95% confidence interval, 0.74 to 0.84; $P < 0.001$) and predictors of LAD receipt included younger age, presence of palpable mobile unilateral inguinal lymph node (cN1), treatment at an academic and/or research center and more recent PC diagnosis. Another study by Joshi et al. identified 1,123 US patients with N+ disease in the National Cancer Database and found that receipt of LAD was an independent predictor of overall survival (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.78; $P < 0.001$) [28]. Although only two-thirds of N+ patients underwent LAD, this report highlights the importance of regional LN surgery in patients exhibiting indication for LAD.

While predictive variables are currently limited, the improved long-term survival in patients at risk of recurrence due to occult micrometastases makes ILND an integral part of standard care. Therefore, early surgical management of regional nodes is strongly recommended with consideration for early referral to high-volume tertiary centers for cases requiring a multidisciplinary approach.

Table 1
Updates of the TNM staging system in penile cancer.

The 4-tiered modification of the Broder's grading system has been replaced by the 3-tiered WHO/ISUP[a] grading system.
Ta is widened to noninvasive localized PSCC.
Perineural invasion and sarcomatoid differentiation are now included to subcategorize T1 disease into T1a and T1b.
Invasion of corpus cavernosum is not considered T2 disease anymore and is categorized as T3 disease while urethral involvement is not considered a factor anymore and can be included in T2 or T3 disease.
pN1 includes $\leq$2 unilateral ILNM without ENE while pN2 includes $\geq$3 or bilateral ILNM without ENE.

[a] ISUP = International Society of Urological Pathology; WHO = World Health Organization.

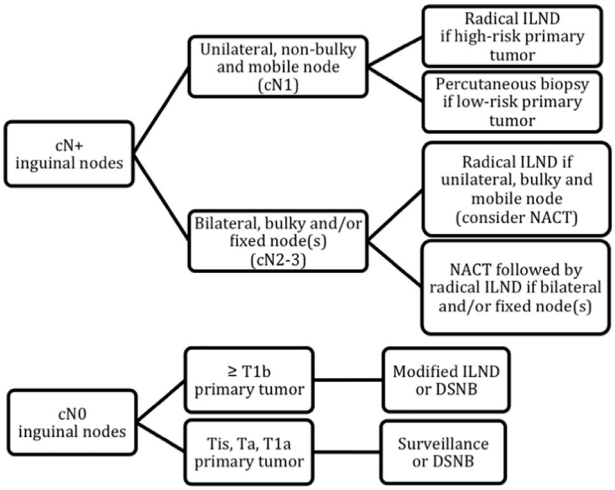

Fig. 1. Management strategies for patients with palpable and nonpalpable inguinal lymph nodes.

Minimizing the morbidity of inguinal lymphadenectomy: Tips and tricks

Recent advances in PC surgical management have resulted in the limitation of the extent of dissection with a trend towards less invasive staging techniques such as sentinel node biopsy and modified-template ILND [15,29]. Surgical morbidity is a significant concern after radical ILND with mainly wound-related complications: wound infection, wound dehiscence, skin flap necrosis and lymphocele [30–34]. A summary of the largest series reporting complication rates in patient cohorts undergoing modified and/or radical ILND is illustrated in Table 2.

Some can result in long-term debilitating sequelae (lymphedema) while some can lead to life-threatening events (thromboembolism and hemorrhage). Several intraoperative and postoperative measures have been proposed to decrease complication rates [29]. Herein we suggest some strategies to reduce morbidity and improve outcomes following ILND.

Lymphocele

Lymphocele formation can be reduced by meticulous control of lymphatics with absorbable sutures or surgical clips throughout the case. The use of hemostatic agents such as fibrin sealants have been examined as a possible adjunct to minimize postoperative morbidity; however, a recent systematic review and meta-analysis revealed no significant reduction of complications after groin dissection with fibrin sealant compared to standard closure technique [35]. Data regarding the use of hemostatic vessel sealing devices for lymphocele prevention remains limited. A retrospective study in gynecologic oncology revealed a decrease in pelvic lymphocele after pelvis lymphadenectomy with the use of electrothermal bipolar vessel sealing device [36]. Conversely, no benefit was noted in reducing postoperative seroma formation in the breast cancer literature [37]. Leaving closed suction drains until drainage is 30 to 50 cc or less per day is preferred. By doing so, fluid accumulation is prevented and thus results in early adhesions between skin flaps and underlying fascia and muscle. Patients can leave the hospital with drains and monitor the outputs daily until subsequent drain removal.

Lymphedema

Saphenous vein preservation whenever possible can reduce the risk of postoperative lymphedema [38]. Recommended postoperative care should include the use of compression stockings and sequential compression devices along with early ambulation and physical therapy. Routine use of fitted stockings during ambulation is preferred until 6 months after surgery with early referral to a specialist if chronic lymphedema develops.

Wound infection

Wound infections can be minimized by proper surgical site sterilization and perioperative prophylactic antibiotics covering groin micro-organisms [39]. We prefer to use postoperative continued oral antibiotics until surgical drains are removed in order to sterilize the port of potential bacteria entry. It is recommended to perform the groin dissection in a delayed fashion, if there is possible concomitant infection of the primary tumor. If

Table 2
Largest series reporting complications after ILND.

Series	Year	# of patients / # of groins	Overall complication rate, no. (%)	Type of complication		Type of LAD (modified vs. radical)
				Minor (%)	Major (%)	
Gopman[26]	2015	327/374	181 (55.4)	119 (65.7)	62 (34.3)	Both
Koifman[27]	2013	170/340	35 (20.6)	25 (71.4)	10 (28.6)	Radical
Stuvier[28]	2013	163/237	95 (58.3)	69 (86.7)	26 (13.3)	Radical
Lopes[29]	1996	145/-	130 (89.9)	- (-)	- (-)	Both
Ravi[30]	1993	112/-	94 (83.9)	- (-)	- (-)	Unknown

needed, the surgical field should be shaved only at the time of surgery to avoid skin infection.

Wound dehiscence and skin flaps necrosis

A horizontal incision just below and parallel to the inguinal ligament should be used instead of the traditional 'S' and 'T'-shaped incisions to minimize the risk of skin flaps necrosis [34,40,41]. Thick skin flaps need to be developed beneath Scarpa's fascia to reduce the risk of ischemia, necrosis and consequent wound dehiscence. Moreover, nonviable or previously irradiated tissues must be debrided to avoid necrosis and dehiscence. Skin rotation flaps and vascularized myocutaneous flaps can be used to cover defects and exposed vessels to reduce postoperative wound-related issues [42]. The most common flaps used include vertical rectus abdominis, pedicled anterolateral thigh flaps or Sartorius, gracilis, and tensor fascia lata flaps [43–45]. Presurgical planning and communication with reconstructive plastic surgery is encouraged in anticipation of extensive groin dissection.

Deep venous thrombosis (DVT)

A simple preventive strategy to minimize the risk of DVT consists in early ambulation for patients undergoing superficial ILND and those with deep ILND without vascularized flap reconstruction. Measures like perioperative antiembolism stockings and sequential compression devices until ambulation can further decrease the risk of DVT. Perioperative prophylaxis with low-molecular weight heparin is to be used in all patients undergoing groin surgery for PC and continued for a month after surgery in those with a history of DVT [46]. Patients with a recent thromboembolic event are recommended to resume therapeutic anticoagulation with low-molecular weight heparin when the risk of bleeding is considered minimal with subsequent return to preoperative anticoagulation medication.

Minimally invasive techniques

Modified inguinal lymphadenectomy

Novel staging techniques have emerged with the aim of minimizing morbidity without compromising oncologic outcomes. In 1988, Catalona proposed a modified template LAD in efforts to minimize the morbidity associated with radical ILND [47]. The boundaries of dissection were limited to the inguinal ligament superiorly, the sartorius muscle laterally, the adductor longus medially, and the fossa ovalis posteriorly (Fig 2). This technique requires a shorter incision and allows the treating physician to preserve the saphenous vein, avoid sartorius muscle transposition and omit the space lateral to the femoral artery and caudal to the fossa ovalis [48]. While fewer complications are associated with this dissection, a modified template must only

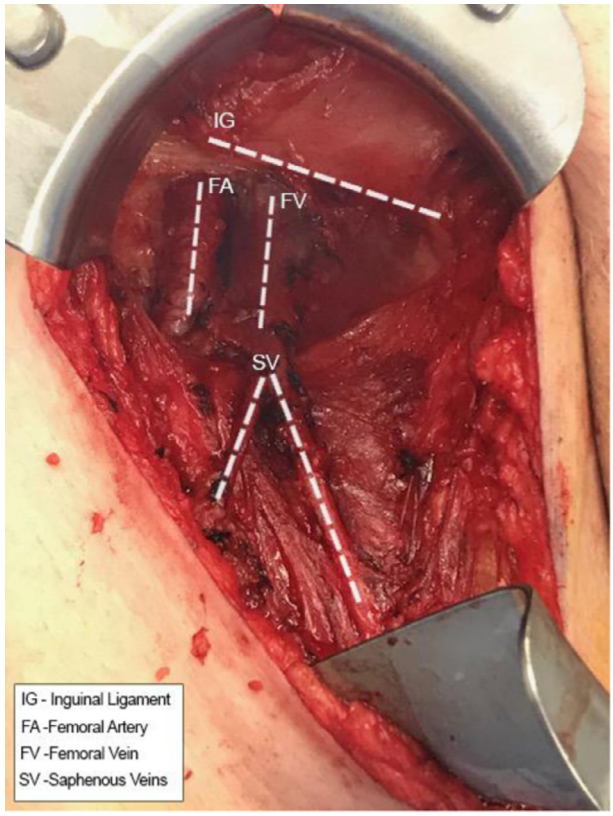

Fig. 2. Surgical anatomy of the inguinal region.

be used in clinically node-negative (cN0) patients with intermediate-/high-risk primary tumors (pT1b/pT2 or greater) as it is primarily a staging procedure [24,49,50]. If intraoperative frozen section reveals nodal involvement, the procedure should be converted to a standard full-template.

Dynamic sentinel node biopsy

DSNB was initially described in PC by Cabanas and later refined by the Netherlands Cancer Institute by combining lymphoscintigraphy, technetium-99m-labeled nanocolloid, and isosulfan blue dye [51,52]. Assuming that PC drains directly into the inguinal sentinel node (SN), DSNB represents a less morbid staging alternative to ILND [53]. Modifications of the technique over the years have led to marked improvements in the false-negative rates (5%) [54]. DSNB should only be performed in high-volume tertiary care centers where at least 20 procedures are done yearly and only be used in intermediate-/high-risk patients with nonpalpable inguinal nodes [15]. If the SN is involved, a standard full-template ILND must be performed.

Minimally invasive lymphadenectomy

Improved implementation of clinical practice guidelines and the use of less invasive staging techniques have led to improved patient selection and reduction in the morbidity

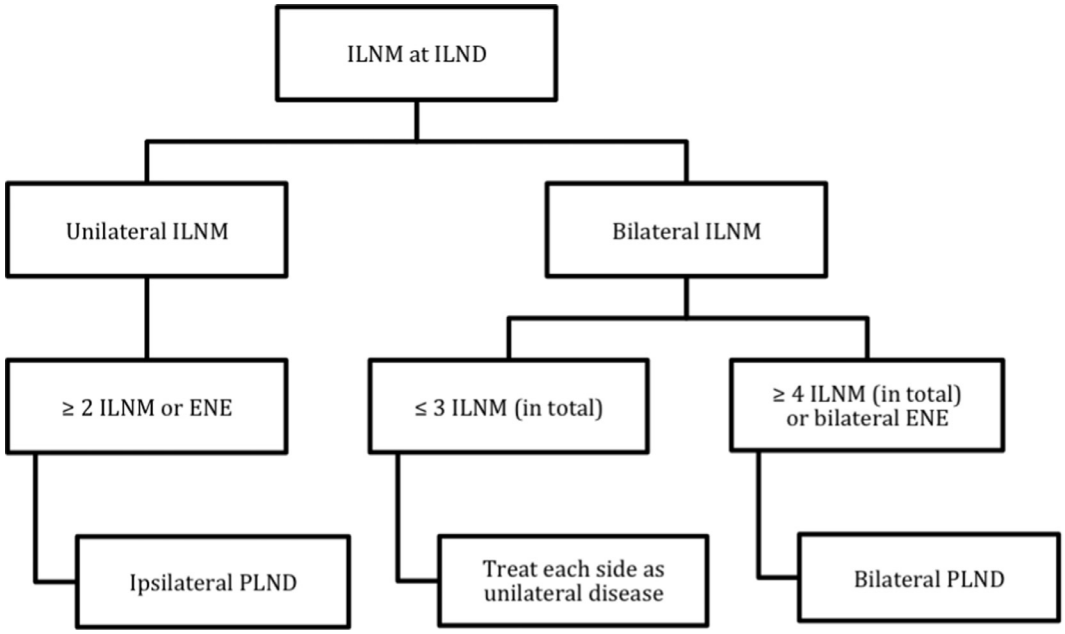

Fig. 3. Management of inguinal lymph node metastasis.

associated with ILND. Yet there is still room for improvements as almost 1 in 2 patients will develop some sort of complication (minor and/or major) after surgery [24].

There are growing reports on the use of minimally invasive LAD in PC since its initial description in 2003. Early series used different laparoscopic approaches for minimally invasive LND: endoscopic subcutaneous modified inguinal lymphadenectomy, video-endoscopic inguinal lymphadenectomy and laparoendoscopic groin dissection [55]. More recently, robot-assisted ILND has gained popularity in the urologic oncology community and demonstrated significant improvements in morbidity while delivering comparable oncologic outcomes [55,56].

Salvage inguinal lymphadenectomy, pelvic lymphadenectomy and extended node dissection in penile cancer

Pelvic LND

PC is known for its stepwise lymphatic spread and the pelvic nodes are the last site of locoregional spread before systemic disease [51,57]. One in 3 patients with inguinal lymph node metastasis (ILNM) will have pelvic involvement [58]. Patients with pelvic lymph node metastasis have a dismal prognosis with a 5-year survival of less than 20% [59,60]. Pelvic lymph node dissections (PLND) in PC should include the external iliac, internal iliac, and obturator nodes [14].

Per National Comprehensive Cancer Network Clinical Practice Guidelines, ipsilateral PLND is recommended in patients with 2 or more ILNM or extranodal extension (ENE) (Fig. 3) [14,61,62]. PLND can be performed at the time of ILND if the intraoperative frozen section is positive for 2 or more ILNM and/or ENE or in a staged fashion if the final pathology of the ILND exhibits high-risk features. A proposed algorithm for the management of enlarged pelvic nodes is shown in Fig. 4.

Salvage ILND

Local recurrence after ILND is associated with poor prognosis [63]. While it has been reported that most local recurrences occur within 2 years of ILND, there is currently no recommendations on the merit of salvage LAD in the setting of inguinal recurrences in the absence of occult disease. Baumgarten et al. reported the largest series of salvage ILND and showed that it can be a curative surgery in carefully selected patients with 9 patients (45%) being free of disease at last follow-up [64]. However, such redo surgery is associated with a significant risk of postoperative complications such as debilitating lymphedema.

Retroperitoneal LND

In highly selected cases with nodal involvement of the retroperitoneum without evidence of distant disease, multimodal therapy including chemotherapy or chemoradiation followed by retroperitoneal LAD in patients with favorable radiographic response was shown to have a curative potential [65]. However, there is currently no evidence-based data to support the use of extended node dissection and collaboration initiatives are needed to assess its value in the setting of isolated nodal disease of the retroperitoneum.

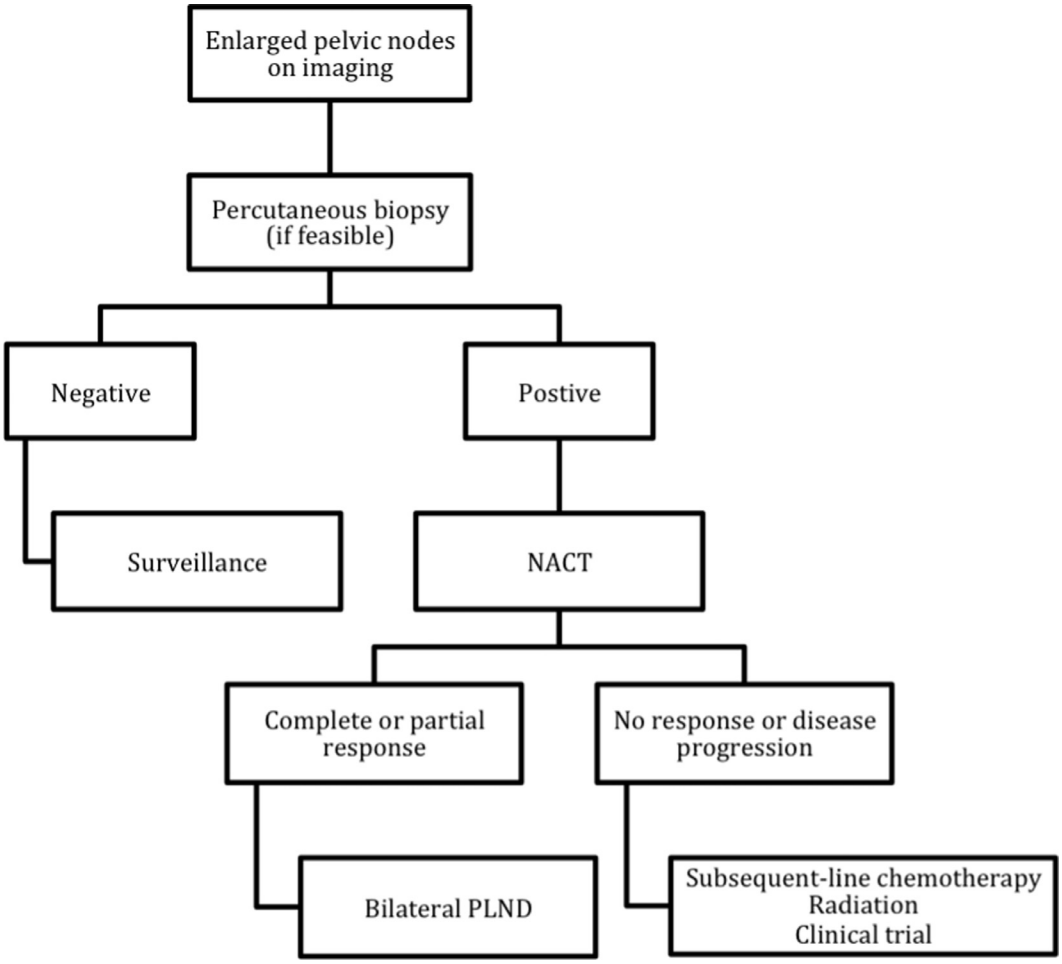

Fig. 4. Management of enlarged pelvic lymph nodes.

Systemic therapy for locally advanced disease

Neoadjuvant chemotherapy prior to ILND or PLND

A multimodal approach rather than surgery alone is preferred in treating patients with locally advanced disease. Current clinical practice guidelines recommend the use of NACT with TIP (Paclitaxel, Ifosfamide, and Cisplatin) prior to ILND in patients with bulky or fixed lymphadenopathy [14] (Fig. 1). In a Phase 2 study, men treated with 4 courses of Paclitaxel, Ifosfamide, and Cisplatin (TIP) had an objective response rate of 50% (15 patients) and a pathologic complete response (pCR) rate of 10% [66]. Other retrospective studies using various NACT regimens reported similar objective response rate and pCR among patients who underwent post-NACT ILND [67,68].

Role of adjuvant chemoradiation

There is currently a lack of evidence for the role of adjuvant chemotherapy in penile cancer with no existing prospective data and only a few limited retrospective studies [69,70]. Per National Comprehensive Cancer Network guidelines, 4 courses of TIP if not given preoperatively can be administered in patients with high-risk features after locoregional surgery such as pelvic lymph node metastasis, ENE and/or bilateral ILNM (level 2A evidence) [14]. A combination of 5-FU and Cisplatin may also be used as an alternative.

A recent systematic review by the European Association of Urology Penile Cancer Guidelines Panel did not show a benefit for adjuvant inguinal radiation in N+ patients after ILND, and therefore, is not recommended as a part of standard clinical practice [71].

What's on the horizon?

The forthcoming prospective, randomized phase III International Penile Advanced Cancer Trial (InPACT) aims to address 2 main questions: does NACT improve survival in patients with locally advanced disease and is there a role for prophylactic PLND in patients at high-risk of relapse after ILND [72]. 400 patients will be enrolled (200 from the United Kingdom and 200 from the United States and Europe) over a 5-year period and will undergo

2 sequential randomizations. In randomization 1 (InPACT-neoadjuvant), patients will be allocated to 3 treatment groups based on disease burden: ILND alone (arm A), NACT (arm B) and neoadjuvant chemoradiotherapy (arm C). In randomization 2 (InPACT-pelvis), men at high-risk of recurrence after ILND will be assigned to either: prophylactic PLND (arm P) or surveillance (arm Q).

Conclusions

LAD remains the cornerstone of surgical management in PC. The advent of novel techniques such as DSNB, modified template ILND and minimally invasive LAD has led to improvements in morbidity and oncologic outcomes. These developments have generated controversy in the urologic oncology community and further collaborative initiatives among high-volume centers are needed to determine the optimal management of regional nodes in PSCC. The InPACT study will surely address some of the many current controversies regarding multimodal management of PC.

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