Management of clinically node-negative groin in patients with penile cancer

Devayani Niyogi, Jarin Noronha, Mahendra Pal, Ganesh Bakshi, Gagan Prakash*

Department of Surgical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India
*E-mail: gagan2311@gmail.com

ABSTRACT

Malignant penile neoplasms are commonly squamous etiology, with the inguinal nodes being the first echelon of spread. The disease spreads to the pelvic lymph nodes only after metastases to the groin nodes, and this is the most important prognostic factor in penile carcinoma. While treatment of penile carcinoma with proven metastases to the inguinal lymph nodes mandates ilioinguinal lymph node dissection, the treatment of patients with impalpable nodes is more controversial. Overtreatment leads to excessive treatment-related morbidity in these patients, while a wait-and-see policy runs the risk of patients presenting with inguinal and distant metastases, which would have been curable at presentation. Unfortunately, no single imaging modality has been proved to be convincingly superior in the staging, and hence, management of the clinically negative groin has been subject to debate. While some high volume centers have promoted the use of dynamic sentinel lymph node biopsy, others advocate the use of the modified inguinal lymph node template to stage the groin adequately. Newer techniques such as video endoscopic inguinal lymph node dissection have been introduced as an alternative to the original radical inguinal lymphadenectomy to reduce morbidity.

INTRODUCTION

Penile cancer is an important health problem in India. The age-adjusted incidence of penile cancer in urban India is 0.7–2.3/100,000 individuals, whereas in rural India, it reaches up to 3/100,000.[1] The most common histological type is squamous cell carcinoma. Other histopathologic types described include verrucous, papillary, squamous, warty, and basaloid.[2] Other histologies include basal cell carcinoma, Paget's disease, leiomyosarcoma, and melanoma.[3]

Lymph node metastasis is the most important prognostic indicator for survival in squamous cell carcinoma of the penis.[4] Patients with low-stage disease, a clinically N0 groin [Table 1], can achieve a 5-year survival of almost 80% with adequate treatment. However, survival declines precipitously as the lymph node burden increases, with a 5-year survival of 0%–17% in patients with N3 disease.[5] A thorough lymphadenectomy in penile cancer offers a chance for cure in low nodal burden disease in contrast to other urological malignancies such as bladder cancer or renal cell carcinoma, where nodal involvement portends poor prognosis and clearance has debatable therapeutic benefit.[6] Meticulous dissection of the groin nodes is important not only for eliminating the disease, but also for appropriate staging, prognostication, and guiding adjuvant treatment.

A radical inguinal dissection is prone to an array of surgical complications. Hence, there is a need to achieve optimal staging, and thereby offer optimum local disease control while avoiding unnecessary groin morbidity. This has been an area of interest and debate in the management of the clinically N0 groin in penile cancer.

Table 1: Definition of clinically N0 groin
1. No palpable/enlarged inguinal nodes
2. No suspicious nodes on ultrasound
3. Palpably enlarged or suspicious nodes that are negative on FNAC

FNAC=Fine-needle aspiration cytology

INCIDENCE OF CLINICALLY N0 GROIN

Diagnosis and treatment of penile cancer in India is often delayed due to associated psychosocial aspects, with a large majority of patients presenting with bulky nodal disease. In world literature, only 20% of patients with penile cancer present with palpable inguinal nodes.[7] This number is as high as 20%–96% in the Indian population.[1] However, in recent years, there is a trend toward a greater proportion of men presenting with clinically impalpable inguinal lymph nodes even in India. Increased awareness and early referrals/better access to health care could be responsible for this change.

ONCOLOGIC IMPLICATION OF ADDRESSING N0 GROIN

The surgeon performs a lymphadenectomy in an N0 groin to provide a precise pathological stage, and thereby guide further treatment as well as to clear microscopic disease, when present. A retrospective series from India found that patients with poor compliance to follow up have improved cancer-specific survival if they undergo an early interval inguinal lymph node dissection (ILND) (at the same admission or within 2 months) when compared to patients undergoing a delayed lymph node dissection (91% vs. 13%, $P = 0.007$).[8] The patients undergoing delayed ILND also had a significantly higher rate of extracapsular extension. Studies from other parts of the world have shown improved survival for patients who underwent early ILND compared to patients undergoing delayed ILND for lymph node metastases detected during surveillance.[9,10]

ROLE OF IMAGING

Clinical examination alone may miss 20%–25% of pathological positive inguinal nodes.[7] Ultrasound (USG) combined with fine-needle aspiration cytology (FNAC) of morphologically suspicious-looking nodes is a useful adjunct to clinical examination, especially in obese and previously irradiated patients with a sensitivity and specificity of 39% and 100%, respectively.[11] However, false-negative rates of FNAC reach up to 15%.[7] Therefore, if clinical suspicion of node positivity is high, and if FNAC is negative, a repeat FNAC or an excision biopsy should be considered. Computed tomography (CT) and magnetic resonance imaging of the abdomen and pelvis have not been found to detect micrometastases reliably and are currently not recommended routinely.[12]

The role of fluorodeoxyglucose-positron emission tomography (PET)/CT in penile cancer was first reported in 2005 by Scher *et al.* Although an initial study showed a sensitivity of 89% and a specificity of 100% for PET scanning, a later study in clinically node-negative penile carcinoma found a low sensitivity, especially in the lymph nodes <10 mm.[13,14] At present, routine imaging with any modality mentioned above is not recommended as per prevailing guidelines but may be employed in certain situations such as obese patients and previously irradiated patients to help in preoperative staging and treatment planning.

ROLE OF PROPHYLACTIC ANTIBIOTICS

Older series have reported that patients with penile cancer harbor infection in a large proportion, as high as 30%–50%.[15] This formed the basis for treating enlarged nodes with prophylactic antibiotics before evaluation. This practice has been given up in the absence of clinically apparent infection because more recent series have reported metastatic involvement in almost 70% of clinically enlarged nodes.[16]

RISK STRATIFICATION OF PENILE CANCER

About 20%–25% of patients harbor occult metastatic disease despite having clinically impalpable inguinal nodes.[17] This number is higher among patients with high-grade disease and with lymphovascular invasion (LVI).[5] In such patients, a thorough inguinal lymphadenectomy offers a chance for cure.

A nonrandomized study of forty patients with T2, T3 penile carcinoma demonstrated a survival benefit in patients undergoing a prophylactic inguinal lymphadenectomy with positive inguinal lymph node metastases as compared to patients who underwent a therapeutic lymphadenectomy for inguinal recurrences detected during close follow-up (3 years cancer specific survival 84% vs. 35%, $P = 0.0017$).[9] On the other hand, radically addressing cN0 groins has its drawbacks. Even in high-volume centers, radical inguinal lymphadenectomy leads to postoperative complication rates between 42% and 57%.[18] Some of these complications, such as wound necrosis and venous thromboembolism, warrant additional surgical procedures and can be particularly debilitating while also delaying adjuvant treatment. Hence, there is a need to find a balance between the aggressive treatment of the cN0 groins and observation. This gave rise to the concept of risk stratification of penile carcinoma.

In a prospective study with 100 patients managed according to the European Association of Urology (EAU) risk stratification [Table 2], after a median follow-up of 29 months, all the patients who were categorized as low risk remained disease-free. However, in 82% of the patients categorized as high risk, the invasive nodal staging was

negative for metastasis;[7] i.e., to pick up 20% of clinically occult nodal metastases, 80% of patients will have to undergo invasive inguinal staging despite having negative nodes. However, given the fact that adequate inguinal staging and clearance can be curative in carcinoma of the penis, this is a caveat that needs to be accepted till more accurate means of inguinal staging can be formulated.

Nomograms for predicting lymph node involvement have been formulated using tumor characteristics such as tumor thickness, growth pattern, grade, LVI, T stage, and cN stage. The nomogram proposed by Ficarra *et al.* showed a good concordance index of 0.876, but a lack of validation in other cohorts precludes its use in daily clinical practice.[19] Figure 1 lists the management schema as per the EUA and NCCN guidelines.

HUMAN PAPILLOMAVIRUS AND MOLECULAR MARKERS IN THE CN0 GROIN

Squamous cell carcinoma of the penis, as reported in Western literature, is associated with human papillomavirus (HPV) infection in up to 50% of the cases.[20, 21] The better prognosis in HPV associated head-and-neck cancers has laid the basis for the de-escalation of therapy in this subset.[22] However, studies in penile cancer failed to show an association between HPV infection and lymph node metastases and 10-year survival rates.[23] HPV-associated penile cancers show extensive levels of tumor-infiltrating lymphocytes (TIL). In addition, programmed death ligand-1

was expressed in high-risk HPV-negative tumors, and the pattern of expression affected lymph node metastases and survival.[24] This is being investigated as a potential area for TIL-based immunotherapy and treatment de-escalation in penile carcinoma as well.[25] In the era of personalized cancer care, molecular profiling of penile cancers may potentially identify patients with occult inguinal disease more accurately, obviating the need for invasive inguinal staging and its associated morbidity.

LYMPHATIC DRAINAGE OF THE PENIS

Lymphatic drainage of the penis encompasses a superficial system that drains the skin and a deeper system that drains the glans and corporal structures.[26] Figure 2 summarizes the following aspects of penile lymphatic drainage:

1. The drainage of the penis is bilateral
2. Rouviere divided the superficial lymphatic system into five zones concerning the saphenous vein draining into the femoral vein: superomedial (i), superolateral (ii), inferomedial (iii), inferolateral (iv), and central (v)[27]
3. Lymphangiographic studies by Cabanas showed the superomedial group to be the first station of draining lymph nodes from the penis
4. The deep inguinal lymphatic system is smaller in size, predominantly located medial to the femoral vessels, deep to the fascia lata. It includes the Cloquet's node located in the femoral canal, which is the gateway of spread to the pelvic nodes
5. Metastases to pelvic nodes skipping the inguinal basin are only anecdotal and can possibly be attributed to inadequate sampling of the inguinal nodes.[28]

OBSERVATION/SURVEILLANCE OF THE GROIN AND PROPHYLACTIC RADIATION

This strategy for the management of the cN0 groin is recommended only in the low-risk group (PTA, pT1a, and G1). Regional recurrences are most commonly seen in the

Table 2: The European Association of Urology risk stratification with chances of lymph node metastases

Risk group	Description	Positive lymph nodes on histopathology (%)
Low	pTis pTa pT1, Grade 1	0
Intermediate	pT1, Grade 2	25%
High	pT2 or higher with Grade 1/Grade 2 any Grade with LVI	42.2%–100%

EAU = European Association of Urology, LVI = Lymphovascular invasion
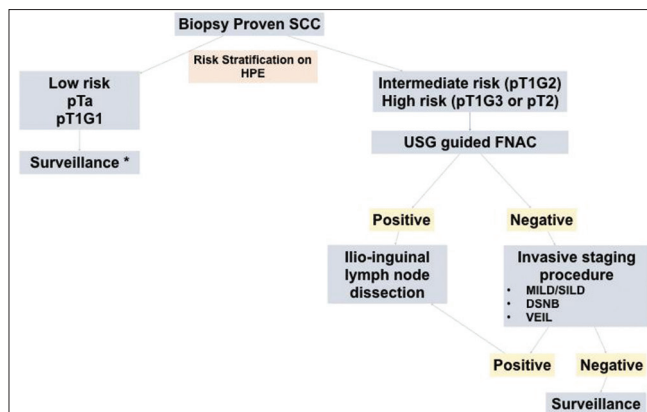

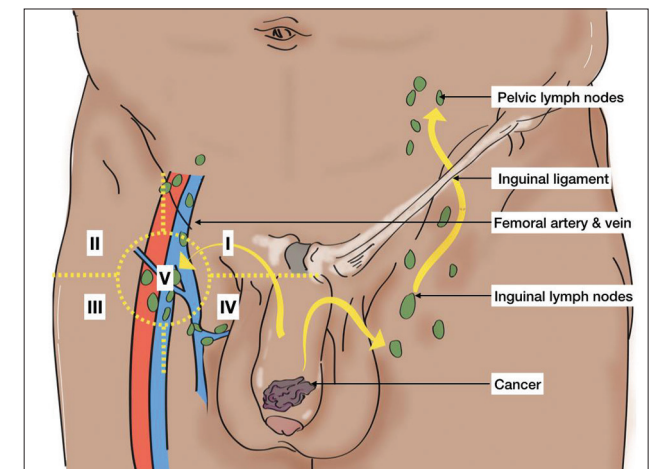**Figure 1:** Schema of management of cN0 Groin as per recent guidelines

Figure 2: Lymphatic drainage of the penis

first 2 years after treatment. The incidence is the highest in patients managed by surveillance (9%) as against those managed by invasive nodal staging or dynamic sentinel node biopsy (DSNB) and found to be pN0 (2.3%). The EAU guidelines suggest 3 monthly clinical examinations for the first 2 years, followed by 6 monthly clinical examinations until 5 years after treatment. Suspicious nodes on palpation must be subjected to FNAC with or without USG guidance. A clinically positive groin on surveillance should be subjected to a unilateral radical inguinal lymphadenectomy. The opposite side, even if clinically disease-free, should be subjected to a modified/superficial groin node dissection or a DSNB.[7]

Radiation therapy has historically been used prophylactically in the N0 groin. A nonrandomized trial from our institution more than two decades back showed a superior 5-year survival for a cN0 groin treated with ILND compared to a cN0 irradiated with 50 Gy to the inguinal-femoral region, 74% vs. 66%, leading it to fall out of favor in clinical practice.[29] With a better understanding of drainage pattern and evolution of radiotherapy techniques, this area could be revisited.

RADICAL INGUINAL LYMPHADENECTOMY

The procedure involves clearing the superficial and deep inguinal nodal basins. Daseler's template is as follows: superiorly by a line joining the anterior superior iliac spine to the pubic tubercle, laterally a line 20 cm down perpendicular to the iliac spine, medially a line 15 cm down perpendicular to the pubic tubercle and inferiorly, a line joining these two points. It involves ligating the saphenous vein and baring the femoral vessels.[30] Median lymph node count in a radical inguinal dissection is 10–11.[31] However, radical lymphadenectomy is associated with major complications such as wound necrosis and deep vein thrombosis in up to 37.5% cases and minor complications such as surgical site infection, limb edema, and seromas in up to 54% of patients.[32] The morbidity of the procedure, especially in patients with low risk of harboring inguinal metastases, led surgeons to search for less invasive methods of staging the cN0 groin.

MODIFIED INGUINAL LYMPHADENECTOMY

To reduce the complications following radical inguinal nodal dissection while maintaining the accuracy of invasive inguinal nodal staging for a clinically N0 groin, a modified template was first proposed by Catalona in 1988.[33] The aim of this template was to remove the nodal stations with the highest probability of being involved (central and superior zones) while minimizing morbidity. No head-to-head randomized trials have been performed comparing radical dissection to the modified template in cN0 disease. According to the NCCN guidelines, frozen section examination of the modified

template is recommended, with completion of the entire radical template if two or more positive nodes are found.[34]

A horizontal—4-5 cm incision parallel to the inguinal ligament is employed. Horizontal incisions are reported to be more in line with the pattern of blood supply and cause less flap necrosis when compared to the vertical or lazy-S incision.[5,7] The template for Modified Inguinal Lymph node Dissection (MILD) is bounded medially by the lateral border of the adductor longus, laterally by the femoral artery, superiorly by the external oblique just above the spermatic cord, and inferiorly by the fascia lata just beyond the fossa ovalis. This template involves the preservation of the saphenous vein and does not include tissue lateral to the femoral artery or distal to the fossa ovalis.[7] The false-negative rate of MIL has been reported to be between 0% and 5.5%, while the morbidity has been reported to be between 10% and 36% making it a standard method of invasive inguinal staging.[34-38]

SUPERFICIAL INGUINAL LYMPHADENECTOMY

Superficial Inguinal Lymph node Dissection (SILD) is performed via a 6–8 cm horizontal incision 1 cm inferior to the inguinal fold. In comparison with the MILD, this procedure involves excision of all the nodal basins superficial to the fascia lata from the adductor longus medially to the sartorius laterally. Like the MILD, the long saphenous vein is preserved. A median lymph node count of 8–10 is achieved.[31] This packet too should be submitted for frozen section analysis, mandating completion if positive nodes are found. Intuitively, SILD has a higher lymph node yield compared to MILD. However, whether this translates into a lower false-negative rate or lower recurrence rate is not yet known.

DYNAMIC SENTINEL NODE BIOPSY

The concept of sentinel node biopsy in penile cancer was first introduced by Cabanas in 1977.[39] Lymphangiographic studies show nodes medial to the superficial epigastric vein as the first echelon draining the penis [Figures 3 and 4]. Involvement of these nodes was a harbinger of inguinal disease and mandated clearance. The concept of sentinel node biopsy was reexplored for melanoma in 1992 by Morton *et al*., who introduced a dynamic component using an injection of isosulfan or patent blue dye to identify individual drainage patterns.[40] In 2000, Horenblas *et al*. lay down the base for the current concept of DSNB in a series of 55 patients, individual mapping was done using Tc-99-labeled sulfur colloid a day before and patent blue on the day of surgery. A sensitivity of 80% was reported, but the high false-negative rates were a cause for concern.[41]

Over the years, the same Netherlands Cancer Institute team has further refined the technique and has suggested the following protocol:[42]

Figure 3: Dynamic sentinel lymph node biopsy – injection of dye

Figure 4: Dynamic sentinel lymph node biopsy – identification of sentinel node

Table 3: Comparison of complication rates

Complication (%)	DSNB	VEIL	MILD/SILD	Radical LND
Skin necrosis	0 13	0	0-4.5	7.5-61
Infection	2.6-13	0	0-14.2	7.5-14.2
DVT	0	0	0	0-12.1
Seroma	1.3	0	12.1-26.3	5-13.8
Edema	1.1-1.7	0	3-20	14.2-22.4
Lymphocele	1.7-21.7	0-23	0-30	2.5-5.2
Major	0-1.3	0	0-14	5-37.5
Minor	6.6-39	20-23	6.8-36.8	45-54

DSNB=Dynamic sentinel node biopsy, VEIL=Video endoscopic inguinal lymphadenectomy, SILD=Superficial inguinal lymphadenectomy, MILD=Modified inguinal lymphadenectomy, LND=Lymph node dissection, DVT=Deep vein thrombosis

1 Intradermal injection of radiolabeled sulfur colloid on the day before surgery with lymphoscintigraphy
2 USG-guided FNAC from palpably enlarged nodes that fail to pick up colloid activity
3 Intradermal injection of patent blue dye just before surgery
4 Using a gamma probe during surgery to identify "hot" nodes
5 Intraoperative palpation of the inguinal region
6 Excision of all "hot," blue and palpable nodes for frozen section examination
7 Exploration of groin when there is no activity on preoperative lymphoscintigram (4%–6%)
8 Serial sectioning and immune-histochemical staining of the nodes instead of routine paraffin sections.

This procedure has proven to be a reliable inguinal staging modality with results comparable to those of DSNB in breast cancer and melanoma where it is standard of care.[7] A prospective multicenter study of 323 patients has shown DSNB to have an impressive sensitivity and specificity of 93% and 100%, respectively. The reported complication rate was <5%, and all complications were managed conservatively.[43] DSNB has a significant learning curve. In a single-center experience, the false-negative rate reduced from 19.2% in the 1994–2001 cohorts to an acceptable 4.8%

in the 2001–2004 cohorts. The complication rate similarly dropped from 10.2% to 5.7%.[44] Hence, DSNB is promoted only in centers with a large volume of experience performing the procedure.[35]

Recently, there is interest in the use of indocyanine green (ICG) labeled colloid for detection of sentinel nodes with a near-infrared fluorescence camera used to detect uptake. This technique, initially described by Brouwer *et al.*, demonstrated a higher number of sentinel lymph nodes (SLNs) detected when ICG-^{99m}Tc nanocolloid was compared to blue dye (96.8% vs. 55.7%; P <.0001).[45] It has been postulated that the easy and fast outflow of blue dye to the next nodal station compared to ICG's outflow led to the lower sensitivity of blue dye. Multiple studies have compared ICG with Tc-labeled radiocolloid and revealed improved SLN detection with ICG.[46-48] This improved optical SLN detection using ICG may subsequently lead to the blue dye being replaced. The additional advantages are low cost, elimination of radioactivity, and documented long-term safety. The disadvantage of ICG is poor penetrance through adipose tissue, requiring skin incision for identification in some obese patients. This technique is still investigational and not yet accepted as the standard of care.

MINIMALLY INVASIVE TECHNIQUES

The high incidence of surgical morbidity following inguinal node dissection deters a large proportion of patients from accepting the procedure. A SEER database analysis revealed that only 25% of all patients who should have received invasive inguinal staging actually receive it.[49] The advent of minimally invasive procedures in other specialties led to the inguinal lymphadenectomy being described using both laparoscopic and robotic approaches.

Video endoscopic inguinal lymphadenectomy (VEIL) was described and reported by Tobias-Machado *et al.* in 2008.[50]

Table 4: Benefits and drawbacks of different staging modalities

Diagnostic technique	Advantages	Disadvantages
Noninvasive (USG/CT/MRI/FDG-PET)	No complications	Poor sensitivity
Minimal invasive (robotic VEIL/DSNB)	Minimum complications	Limited availability, learning curve, expensive equipment
Invasive (MILD/SILD/radical ILND)	High sensitivity can be performed at any center	High complication rate

USG=Ultrasound, CT=Computed tomography, MRI=Magnetic resonance imaging, FDG-PET=Fluorodeoxyglucose-positron emission tomography, VEIL=Video endoscopic inguinal lymphadenectomy, DSNB=Dynamic sentinel node biopsy, ILND=Inguinal lymph node dissection, MILD=Modified inguinal lymphadenectomy, SILD=Superficial inguinal lymphadenectomy

Table 5: Unanswered questions in the management of N0 groin

1. Imaging modality to be used to stage the cN0 groin
2. Adequacy of template (MILD or SILD) during invasive staging
3. Long term oncologic outcomes in minimally invasive procedures
4. Choice of agent (Patent blue, Tc nanocolloid, ICG), dual or triple tracer for DSNB
5. Duration of follow-up in groins kept on surveillance

MILD=Modified inguinal lymphadenectomy, SILD=Superficial inguinal lymphadenectomy, ICG=Indocyanine green, DSNB=Dynamic sentinel node biopsy

VEIL encompasses a laparoscopic performance of radical inguinal lymphadenectomy with the sacrifice of the great saphenous vein. This procedure showed similar lymph node yield and comparable oncological outcome to an open procedure at a median follow-up of 33 months.[51] The VEIL arm had significantly less morbidity (20% vs. 70%, $P=0.015$) and reduced hospital stay (24 h vs. 6.4 days).

Sotelo *et al*. reported outcomes of the endoscopic ILND for penile carcinoma in 2009. This technique utilized the MILD template, preserving the saphenous vein and deep inguinal nodes were cleared only if frozen section analysis showed positive nodes. This technique too showed decreased surgical complications without affecting the oncologic outcome in their preliminary results.[52]

A Phase 1 study for robotic-assisted VEIL (RAVEIL) was reported by Matin *et al*. in 2013. After performing RAVEIL, a small incision was made to check the adequacy of clearance achieved. RAVEIL achieved adequate clearance with acceptable lymph node yield as compared to an open procedure. Due to the incision placed to check clearance, this study could not comment upon the difference in surgical morbidity.[53] A study from India reported long-term lymphedema in 4 out of the 22 patients with one recurrence (5.2%) in pathological N0 groin during follow-up.[54]

A more recent large study from India has confirmed oncological safety of Robotic assisted groin node dissection and found that the benefit compared to open is more pronounced for non bulky lymph node positive groins.[55] Given the dramatic decrease in surgical morbidity, equivalent nodal yield, and comparable short-term oncologic outcomes, these endoscopic procedures have been widely accepted. The complication rates between different procedures as described in the literature have been listed in Table 3, while Table 4 describes the benefits and drawbacks of each modality of staging the cN0 groin.

RELEVANCE OF CHANGES IN THE RECENT AMERICAN JOINT COMMITTEE ON CANCER 8 STAGING

1. pT1 corresponds to disease in the subepithelial connective tissue. T1b disease includes cases with Grade 3 histology, presence of LVI, perineural invasion, or sarcomatoid histology. T1b disease has a higher chance of metastasis to lymph nodes (33.3%–50% in T1b vs. 10.5%–18.1% in T1a) and warrants invasive inguinal staging[56,57]
2. In American Joint Committee on Cancer 7, involvement of corpus spongiosum or cavernosa was staged as T2 and urethral involvement comprised T3 disease. It was observed that cavernosal involvement was associated with higher inguinal lymph node involvement as compared to corpus spongiosum alone (48.6%–52.5% vs. 33%–35.8%). Hence, involvement of corpus spongiosum alone is now categorized as pT2, and cavernosal involvement upstages the disease to pT3.[56,58]

CONCLUSION

As of today, all intermediate- and high-risk groups with cN0 groins should undergo invasive inguinal staging in the form of MILD/SILD, DSNB, or VEIL even if the FNAC shows no metastases. Those with positive nodes on frozen section analysis should undergo a complete clearance. Surveillance may be offered as an option only for low-risk groups amenable to regular follow-up.[34,35] A lack of large randomized controlled trials, the heterogeneity of patient groups with cN0 groin, and lack of any meta-analysis have limited the formation of stringent guidelines. With many unanswered questions in the management of the cN0 groin [Table 5], there is a need for multicenter collaboration to provide Level 1 evidence-based guidelines for penile cancer patients with cN0 groin. Global initiatives like the InPACT study for locally advanced penile carcinomas are the way forward for answering questions for this rare cancer.[59] India should take the lead in initiating similar multicenter trials planned across high volume centers to determine the standard of care for addressing groins in penile cancer patients.

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