



Management of the Clinically Negative (cN0) Groin Penile Cancer Patient: A Review

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To determine the role of noninvasive, minimally invasive diagnostic modalities and current management recommendations for cN0 PNC, a literature review using PubMed and Web of Science search engines were conducted. We found that for predicting ILN+: physical exam has limitations, nomograms are not validated, conventional computerized tomography/magnetic resonance imaging/positron imaging tomography scans have minimal role, and dynamic sentinel lymph node biopsy is the most reliable minimally invasive modality. Adverse pathological features: G3, stage \geq T2, presence of LVI, and rare histopathological variants are important predictors of ILN+ and their presence warrants prophylactic ILND or dynamic sentinel lymph node biopsy. In the absence of these adverse pathological features conservative management is justified. *UROLOGY* 131: 5–13, 2019. © 2019 Elsevier Inc.

Inguinal lymph node metastasis (ILN+) from penile cancer (PNC) is the worst predictor of patient survival. While the 5-year survival rate of PNC patients without ILN+ is 85%, for those patients with ILN+ it is only 59%.¹ There is controversy whether inguinal lymph node dissection (ILND) should be offered early in the course of the disease in patients with clinically negative groin exam (cN0) or delayed until palpable ILN develops. Patients with cN0, received early ILND had a 3-year survival rate of 84% compared to 35% for those received delayed ILND and the incidence of extra-nodal extension was 20% compared to 95% in the early vs delayed ILND groups, respectively.² A delay in ILND \geq 3 months in a group of 84 PNC patients of whom 47 (56%) were cN0, in the cN0 patients, the 5-year disease specific survival rate was 78.6% for early (\leq 3 months) dissection compared to 45.8% for late ($>$ 3 months) dissection.³ Also, demographic and socioeconomic factors were found as driving factors for early vs delayed ILND.⁴ To further compound the decision of early vs late ILND in the cN0 patient; significant inter observer variability exists among uro-pathologists with variation in reporting tumor grade and stage. In one European multicenter study, 11 experienced uro-pathologists were asked to review 90 PNC specimens and the percentage of Grade 1 tumors assigned ranged from 8.6 to 52.5%, Grade 2 tumors from 27.1 to 72.6%, and Grade 3 tumors from 11.7 to 48.7%.⁵

Although there are several studies that stress the value of noninvasive and minimally invasive staging technique to determine the LN status of PNC patients, they are yet to be of utmost accuracy.⁶ The nomogram developed by Ficarra et al have showed good concordance index (0.876), however it has not been validated independently.⁷ Conventional computerized tomography (CT) scan and magnetic resonance imaging (MRI) lack adequate sensitivity and specificity in detecting micrometastasis in the cN0 PNC patient.⁸ Dynamic sentinel lymph node biopsy (DSLNB) is a minimally invasive modality that showed good results in detecting micrometastasis in patients with cN0 disease in centers experienced in performing this procedure.⁹

Concerns regarding offering early ILND in cN0 stems from the facts that (1) ILN+ is present in 18%-25% of the cN0 and consequently the procedure may be an overtreatment in 75% or more of those patients.¹⁰ (2) ILND has been traditionally a morbid procedure. Contemporary literature revealed a complication rate of 19% and 27% for minor and major complications, respectively in diagnostic ILND in cN0 patients and a complication rate of 7% in DSLNB.¹¹ In this review we will provide the best evidence regarding the role of noninvasive and minimally invasive LN staging modalities, role of molecular markers, role of nomograms, risk stratification and indications of intervention vs watchful waiting, and outcomes in the cN0 PNC patient.

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METHODS

PubMed and Web of Science were searched for relevant articles. A blended strategy was built in PubMed using Medical Subject Headings terms (penile neoplasms and sentinel lymph node biopsy) and text words/phrases in the titles and abstracts (“PNC,” “penile neoplasms,” “penile carcinoma,” “clinically

negative," "node negative," cN0, lymphadenectomy, "sentinel node," "sentinel nodes," "node dissection," ("lymph node(s)" AND (radiation OR irradiation)). The Web of Science search consisted of the text words/phrases searched with the topic designation. No date limitation was imposed on the searches; the results were limited to English language articles. Abstracts were reviewed by two authors (MHK and MIK). Two major guidelines in PNC; the National Comprehensive Cancer Network (NCCN), and the European Association of Urology (EAU) guidelines were reviewed and recommendations in cN0 PNC patients were summarized (study flow chart is provided in supplementary material). Overall, the quality of evidence was low and consequently it was felt a narrative rather than a systematic review is more appropriate.

RESULTS

Initial search resulted in 558 articles. Following initial screening, 454 titles were excluded. Of the remaining 147 articles that were studied in detail; we excluded 98 articles that were duplicates, articles in non-English language, case reports, and low level of evidence. The remaining 50 articles formed the basis of this review. Overall, there were no randomized studies, many studies were from institutional well-maintained prospective PNC data bases and overall the numbers of patients included in the studies were not large.

Noninvasive LN Staging in the cN0 PNC Patient

Role of Physical Exam in LN Staging of the cN0 PNC Patient. Physical exam of the groin should be performed in all PNC patients. However, there are possible challenges as obesity and previous inguinal surgery, all may make physical exam difficult. Also, enlarged ILN secondary to infection of the primary tumor rather than metastasis can occur in up to 50% of patients, while 20% of patients with cN0 may have ILN+. Horenblas et al conducted a study on 102 PNC patients that has grade IV evidence. The authors reported 82% sensitivity and 79% specificity for clinical exam of the groin. The same authors reported an under staging in 10% and over staging in 16% of patients.¹² In the setting of the above-mentioned limitations, imaging of the groin with ultrasound (US), CT scan, or MRI should be considered. MRI can provide information on both the primary penile tumor depth of invasion (T stage) and the status of groin LN (N stage).¹³

Role of Tumor Markers in LN Staging of the cN0 PNC Patient. In the setting of PNC, there is evidence supporting the role of changes that occur in certain genes and their encoded products which subsequently enable cancer cell metastasis. Moreover, tumor marker profiles with different biological roles have role in the assessment of patient's prognosis.¹⁴⁻¹⁶ The over expression of p53 which is present in 42% of PNC was an independent predictor of ILN+ and poor survival.¹⁷ The prognostic significance of p53, Ki-67, PCNA, E-Cadherin, and Matrix Metalloproteases-9 was evaluated in PNC as possible predictors of aggressive disease with increased risk of metastasis.¹⁸ The expression of Ki67 and PCNA were associated with increased risk of ILN+.¹⁹ MYC is a proto-oncogene encodes target genes controlling key cellular functions including cell growth, cell cycle progression, and DNA replication. Derangement of MYC function, leads to aggressive tumor with increased risk of metastasis and poor outcome.²⁰ KAI1/CD82 downregulation was associated with increased risk of ILN+.²¹ Also negative p16 immunohistochemistry, as evidenced

by allelic loss near the p16 (INK4A) locus and/or hypermethylation of the p16 (INK4A) promoter was associated with increased risk of ILN+. Negative p16 immunohistochemistry can be present in 62% of PNC patients and is linked to human papilloma virus DNA.²²

However, the role of molecular markers is still evolving. Also; likely a panel of these markers will be more useful than using individual markers. We summarized the tumor markers that may have prognostic significance in predicting ILN+, alone or as a panel of markers in [Table 1](#).

Role of Nomograms in LN Staging of the cN0 PNC Patient.

Nomograms have been designed to predict ILN+ in the cN0 PNC patient. Ficarra et al proposed a nomogram using 8 clinical and pathological variables including clinical stage of LN, tumor thickness, microscopic growth pattern, histologic grade, vascular invasion and invasion of corpus spongiosum, corpus cavernosum, and urethra.²³ Nomogram based on pathological criteria and incorporating molecular markers as p53 expression were also proposed. However, these nomograms were not externally validated and as such their use in clinical practice is not popular.¹⁰

Role of Imaging in LN Staging of the cN0 PNC Patient.

Unlike other genitourinary cancers where imaging can accurately detect metastasis in patients with low-stage disease; PNC represents a challenge for these imaging modalities. The situation is compounded by the rarity of the disease which does not allow clinical studies on large group of patients and testing new imaging modalities that were proven useful in other cancers.

Groin US. Groin US uses a high resolution 7.5 or 10 MHz probe. It relies on the detection of a distortion in the normal architecture of the involved LN which is detected prior to the LN enlargement. However, because of the overlap between benign and malignant features of distorted LN architecture, groin US is usually combined with fine needle aspiration cytology (FNAC) of the sonographically abnormal LN. If the FNAC returns positive, ILND is indicated. Kroon et al studied US + FNAC in 83 cN0 patients as an initial investigation prior to DSLNB. A total of 49/83 groins were negative on US and underwent DSLNB. A total of 34/83 groins were suspicious on US and consequently all had FNAC. A total of 9/34 were positive on FNAC. The reported sensitivity and specificity were 39% and 100%, respectively. In this report US + FNAC reduced the need for DSLNB by 11%.²⁴ However, groin US has several limitations. The sensitivity is low, FNAC can only detect metastasis >2 mm and it is reported to have a false negative rate of 29%.²⁵

Conventional Abdominal and Pelvic CT Scan/MRI. Conventional CT/MRI scan rarely detect micrometastasis in patients with cN0 disease.²⁶ CT/MRI rely on size criteria of the LN (>8-10 mm). Also, inflammatory changes associated with the primary tumor may cause enlargement of the ILN. These imaging modalities, in the cN0 patient, are indicated if the physical exam is difficult. Lucchesi et al showed an incremental value to physical groin exam in detecting ILN+ using the MRI. While the clinical exam accurately staged the LN in 7/15 (46.7%) patients, the MRI accurately staged 13/15 (86.7%).²⁷ Conventional CT and MRI have an additional role in the cN0 patients who are intermediate or high risks for ILN+, and consequently will be offered prophylactic ILND, however this will be for staging purposes.^{10,13}

Table 1. Tumor markers thought to predict increased risk of lymph node metastasis.

(A) Individual Markers That May Predict ILN+					
Marker	Location	Function	Anomaly	HPV Relation	Outcome in cNO
p 53 ^{14,15}	17p13.1	Tumor suppressor gene	Mutation leads to uninhibited cell growth	P53+HPV DNA → worse cancer specific survival	Increased risk of ILN+
Ki67 ¹⁶⁻¹⁸	Nuclear matrix protein	Role in cell cycle progression	Overexpression	N/A	Controversial: -Increased risk of ILN+ ¹⁶ -No increased risk of ILN+ ^{17,18}
PCNA ¹⁹	Nucleus	Role in cell proliferation	Overexpression	N/A	Increased risk of ILN+
C-reactive protein ²⁰	Produced in liver and present in serum	Produced in response to inflammation	Increased serum level	N/A	Increased risk of ILN+
E-cadherin ²¹	Trans-membrane Protein	Maintaining cellular adhesion and signal transduction	Low level	N/A	Increased risk of ILN +
Squamous cell carcinoma antigen ²²	Serum	Serum glycoprotein	Increased absolute level or continuous rise after penectomy	N/A	Increased risk of LN+
MYC ²³	8q 24	Proto-oncogene Regulate cellular proliferation	Numerical aberrations (gains) or expression in >30% of primary tumor cells	N/A	Increased risk of ILN+
Matrix metalloproteases-9 (MMP-9) ²¹	Basement membrane	Group of enzymes that degrade type IV collagen in the basement membrane and involved in invasion mechanism	Increased immunoreactivity	N/A	Increased risk of ILN+
(B) Studies reporting on panel of tumor markers					
Study	Combination	End points	Outcome		
*Zhu et al ¹⁷	-p53, Ki-67, E-cadherin and MMP-9	- CSS - LN+	-p53 overexpression was associated with ↓ survival and ↑ risk of ILN+		
↓Gunia et al ¹⁵	-p53, p21 and Cyclin D1	- CSS	-p53 overexpression was associated with ↓ survival		
¶Campos et al ²¹	MMP-2, MMP-9 and E-cadherin	- CSS - LN+	-↓ E-cadherin was associated with ↑ risk of ILN+ - ↑ MMP-9 was associated with ↓ survival		
•Guimaraes et al ¹⁹	PCNA and MIB-1/Ki-67	- CSS - LN+	- Overexpression of PCNA and MIB-1/Ki-67 was associated with ↑ risk of ILN+ - No effect of these markers on survival		
×Protzel et al ²⁴	KAI1/CD82	- CSS - LN+	- Low expression was associated with ↑ risk of ILN + and ↓ survival		

CSS, cancer specific survival; CD82, cluster of differentiation 82; HPV, human papilloma virus; ILN+, Inguinal lymph node metastasis; KAI1, Kang-ai 1; LN, lymph node; MMP-2, matrix metalloproteases-2; MMP-9, matrix metalloproteases-9; N/A, not available data to document correlation or there may be no correlation at all; PCNA, proliferating cell nuclear antigen.

* On univariate analysis Ki-67 was associated with increased risk of ILN+ but on multivariable analysis this effect was not demonstrated.

↓ CyclinD1 and p21 expression were not associated with worse survival. However, adding p21 to the multivariable model improved the predictability of the model to survival.

¶ On multivariable analysis neither E-cadherin predicted ILN+ nor MMP-9 predicted poor survival.

• On multivariable analysis, PCNA continued to predict ILN+ but not MIB-1/Ki-67.

× The presence of HPV-DNA was associated with low expression of KAI1/CD82 and consequently poor survival.

Positron Imaging Tomography/PET/CT. Positron Imaging Tomography (PET)/CT combines functional information derived from the uptake of 18F-fluorodeoxyglucose by the abnormal LN with the anatomical information provided with the low-dose CT scan. Sadeghi et al conducted a meta-analysis on the role of PET/CT in the cN0 patients and sensitivity was only 56.5%. Also, the technique has the limitations of difficulty to identify metastatic disease <10 mm and to differentiate between inflammation and metastatic deposits.²⁸ In summary, there is likely a minimal to no role of PET/CT among PNC patients with cN0 disease unless a suspicious nodal area is seen on CT/MRI and is not amenable to image-guided biopsy.

Single Photon Emission Computerized Tomography-CT. In this imaging technique, ^{99m}technetium (^{99m}Tc) nanocolloid is injected directly into the primary tumor or just proximal to the surgical scar in 4 points. A gamma camera is used to detect the photon emission from the sentinel lymph node (SLN) in the groin using both dynamic (20 minutes) and early and delayed static images (5 and 120 minutes) postinjections. This functional information is overlapped with conventional CT imaging to provide a 3D CT image to identify the first drainage basin and to facilitate SLNB. Preliminary data are encouraging. Lutzen et al. studied 25 patients with cN0 who underwent Single Photon Emission Computerized Tomography (SPECT)/CT to facilitate SLNB. The authors reported a sensitivity and specificity of 88.8% and 86.7% respectively.²⁹

Lymphotropic Nanoparticle Enhanced Magnetic Resonance Imaging (LNMRI). This new imaging modality relies on the presence of macrophages in the normal LN that engulf the injected nanoparticles and will appear dark on T2 weighted MRI. Metastatic LN lacks these macrophages and consequently the nanoparticles are not concentrated in the malignant LN that will appear bright. Tabatabaei et al. correlated the LNMRI and pathological LN findings in 113 LN excised from 7 patients. Of these patients, 5 were cN0. Overall 13/113 LN were positive and reported a sensitivity, specificity of 100% and 97% respectively.³⁰ Despite good results, the study population was small with no long term follow up.

Minimally Invasive LN Staging in the cN0 PNC Patient

Lymphoscintigraphy and Static Sentinel Lymph Node Biopsy. Anatomically, the SLN is located close to the superficial epigastric vein. The SLN area is comprised of ≤7 LN. The SLN is the first lymph drainage area to the penis and consequently if it is negative, further LN dissection is discouraged.³¹

Technique: A 5-cm incision, 2 finger breadths lateral and inferior to the pubic tubercle is made. This is followed by inserting a finger in an upward and medial direction toward the pubic tubercle to excise all the lymphatic tissue. However, the technique of static sentinel lymph node biopsy (SSLNB) is associated with a high false negative rate and the technique of SSLNB has been largely abandoned.³² Of note, in PNC involving the gland (34.5% of all PNC), glandular lymphatics may bypass the superficial ILN and drain directly to the deep ILN or pelvic LN.³³

Dynamic Sentinel Lymph Node Biopsy. The technique of DSLNB is more popular in Europe than the United States. DSLNB reduces the high false negative rate of SSLNB, by combining functional and anatomic information to better identify

the SLN. DSLNB is thought to have no role in clinically palpable LN.

Technique: In DSLNB, intradermal injection of hybrid tracer of ^{99m}Tc around the tumor is performed; this is followed by acquiring dynamic images at 10 minutes after injection on a coronal view, 30 minutes then 2 hours by dual-head gamma camera. A gamma probe is used to detect the SLN and at the beginning of the surgical procedure, patent blue dye is injected that will be taken up by the SLN to add visualization. The SLN are then removed and if positive radical ILND is performed. The reported false negative rate with this DSLNB technique is 25%.⁹

Technical considerations and modifications to the standard technique of DSLNB in cN0:

1. DSLNB is commonly performed at the time of penile surgery. However, delayed DSLNB is a feasible procedure and excision of the primary tumor does not seem to change lymphatic drainage.³⁴
2. Ideally, bilateral SNL are visualized. However; the nonvisualization rate in DSLNB is 12%. It is recommended in this situation to repeat the DSLNB technique. However; if the nonvisualization of SNL continues, patient with favorable pathological criteria (≤T1aG1-tumor invading subepithelial tissue and no lymphovascular invasion [LVI]) can be put on active surveillance and those with unfavorable histologic characteristics (≥T1G2) can be offered superficial LN dissection with intraoperative frozen section.³⁵
3. Repeat DSLNB is feasible despite previous SNB and the detection rate of SNL in this clinical scenario is 79%.³⁶
4. Patients with micrometastasis (<2 mm) in SNL were unlikely to have additional nodal involvement in one report.³⁷
5. A new modification is the use of hybrid radioactive and fluorescence tracer indocyanine green – ^{99m}Tc – nanocolloid instead of the traditional patent blue. The new hybrid showed better tissue penetration and visualization with 95% of SLN detected compared to 54% using traditional patent blue.³⁸
6. Combining groin US with or without FNAC and DSLNB improved the sensitivity of DSLNB to 95%.³⁹
7. Combining SPECT-CT with DSLNB improves its sensitivity to 88.8% and shortens the duration as well.⁴⁰
8. Using modifications to the DSLNB technique, and in experienced centers, the contemporary reported false negative rate is only 4.8% and complication rate of 5.7% in the cN0 patient.⁴¹

Invasive LN Staging in the cN0 PNC Patient

Risk Stratification for ILN+ in the cN0 PNC Patient. Pathological findings in the primary tumor are of paramount importance in the decision-making on performing prophylactic ILND. Slaton et al reported the risk of ILN+ to be 64% in pathological

stage \geq T2, 55% in the setting of vascular invasion, and 61% in tumors exhibiting $>$ 50% of the G3 disease.⁴² Solsona et al classified patients into 3 risk groups for developing ILN+ based on tumor stage and grade.⁴³ These risk groups were (1) *Low risk*: comprising patients with T1 and G1 tumors and the incidence of ILN+ was 0% in this group. (2) *Intermediate risk*: comprising T1 and G2-G3 or T2-3 and G1 tumors and the incidence of ILN+ was 36.4%. (3) *High risk*: comprising patients with T2-3 and G2-3 tumors and the incidence of ILN+ was 80%. Such studies had important implications on the management of PNC. The most recent (8th edition, 2016) tumor node metastasis staging for PNC was modified to reflect the increased risk of ILN+ in T1 (tumor invades dermis, lamina propria, and dartos fascia) patients with LVI and poorly differentiated cancer (G3) as stage T1b.

The NCCN Guidelines Recommendations for Invasive or Minimally Invasive ILN Staging in the cN0 PNC Patient. The NCCN guidelines identified these pathological features as high risk for ILN+ and consequently warrant prophylactic ILND in patients who are cN0. These features are (1)

presence of LVI, (2) T1 G3, (3) \geq T2 any grade, and (4) $>$ 50% G3 tumors.¹³

The EAU Guidelines Recommendations for Invasive or Minimally Invasive ILN Staging in the cN0 PNC Patient. The EAU classified cN0 patients into 3 risk categories for developing ILN+.¹⁰ These risk groups are:

- 1) Low risk for ILN+: Comprising tumors that are Tis (in situ), Ta (noninvasive), and T1a (tumor invades dermis, lamina propria and dartos fascia and no LVI or G3).
- 2) Intermediate risk for ILN+: Comprising T1b (LVI or G3) tumors.
- 3) High risk for ILN+: This includes any G3 tumors or stage \geq T2 PNC.¹⁰

After examining these 2 guidelines, one can conclude that the high-risk pathological features reported in the NCCN guidelines coincide with the intermediate and high-risk groups of the

Table 2. Summary of recommendations on utilization of diagnostic modalities and management strategies in the cN0 penile cancer patient.

Diagnostic Modality	Recommendation	GR
(A) Noninvasive modalities		
1- Groin physical exam	- Perform in all patients	C
2- Tumor markers	- Preferably a panel of markers	C
3- Nomograms	- Limited role in predicting ILN+	D
4- Groin ultrasound	- Limited role in predicting ILN+ as a standalone tool	D
	- Combine with FNAC to improve sensitivity and specificity	C
	- Combine with DSLNB with or without FNAC to increase sensitivity	
5- Conventional CT/MRI	- Perform if physical exam is difficult	C
	- Perform for cancer staging prior to ILND	
6- PET/CT scan	- Limited role in predicting ILN+	C
	- Possible role in suspicious CT/MRI findings not amenable to percutaneous biopsy	
7- SPECT-CT	- Limited role in predicting ILN+	D
	- Can be combined with DSLNB to improve sensitivity and shorten procedure time	
8- LNMRI	- Limited role in predicting ILN+	D
(B) Minimally invasive modalities		
1- DSLNB	- Currently most reliable minimally invasive staging modality in predicting ILN+	B
	- Replaced SSLNB	
Management Strategy		
	Indications	*GR
1- Conservative management	- T1G1 - TaG1 - CIS - Histopathological variants (verrucous, warty, and papillary)	B
2- Prophylactic ILND or DSLNB	- G3 (\geq 50%) - Stage \geq T2 - +LVI - Rare histopathological variants (baseloid, sarcomatoid, and adenosquamous)	B
3- Prophylactic ILN radiation	- May be considered in high risk patient not fit for surgery	D

CT, computerized tomography; DSLNB, dynamic sentinel lymph node biopsy; FNAC, fine needle aspiration cytology; G, tumor grade; GR, grade of recommendation; ILND, Inguinal lymph node dissection; ILN+, positive inguinal lymph nodes; LNMRI, lymphotropic nanoparticle-enhanced magnetic resonance imaging; LVI, lymphovascular invasion; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computerized tomography; SPECT/CT, single photon emission computerized tomography; SSLNB, static sentinel lymph node biopsy.

EAU guidelines. The presence of these features warrants prophylactic ILND. In the absence of these high-risk features active surveillance is recommended.

The Controversy Surrounding LN Management in the T1G2 cN0 PNC Patient. There is a debate on performing ILND in the T1G2 cN0 patients. If this T1G2 tumor exhibits LVI, this will be stage T1b disease and prophylactic ILND is recommended.^{10,13} However, the guidelines are not clear in the T1G2 tumor that does not exhibit LVI; stage T1a G2. Thuret et al reported 5-year cancer specific mortality of 2.6%, 10%, and 15.9% for T1G1, T1G2, and T1G3 tumors, respectively and without ILND ($P < 0.05$).⁴⁴ However, owing to the limitations of the used data set, pathological criteria as LVI and or perineural invasion could not be counted for. It is reasonable in T1aG2 to individualize the decision based on the overall general health of the patient and the risk of developing complications following ILND or to perform DSLNB or superficial ILND with intraoperative frozen section (Table 2).

Type of ILN Staging in the cN0 PNC Patient. Anatomic Considerations. Zonal anatomy of superficial ILN: Daseler in the forties of the last century, described the superficial ILN to be present in close proximity to the saphenous vein with a quadrilateral area with its superior boundary being a 12-cm line extending between the pubic tubercle medially and the anterior superior iliac spine laterally, 1 cm above the inguinal ligament. The medial boundary is a vertical line extending 15 cm caudally from the pubic tubercle and the lateral boundary is a vertical line extending 20 cm caudally from the anterior superior iliac spine. The inferior boundary is 11 cm in length joining the medial and lateral boundaries. This quadrilateral area is centered on the junction of the saphenous and femoral veins and is further divided into superomedial,

superolateral, infromedial, infrolateral zones, and a central zone at the junction of the saphenous and femoral veins. Most of the lymphatic drainage to the superficial ILN is to superomedial and central zones and to a lesser extent infromedial zone.³³ (Fig. 1).

Zonal anatomy of deep ILN: The deep ILN are usually 1-3 LN in number. These LNs lie deep to the fascia lata and medial to the femoral vein. The most common deep ILN is found in the femoral canal between the femoral vein and the lacunar ligament (at the medial portion of the inguinal ligament)- the node of Cloquet.³³

For the intermediate and high-risk groups for ILN+, several approaches for ILN staging were recommended:

- 1) Modified ILND: Where the saphenous vein is preserved and the lateral and caudal extents of ILND are reduced; excision of superficial and deep inguinal lymphatic tissue is performed and particularly the medial and central lymphatic tissue (Fig. 1).
- 2) Performing DSLNB to be followed by superficial and deep ILND if ILN+.

Performing superficial ILND with intraoperative frozen section and if the frozen section is positive for metastasis, bilateral superficial, and deep ILND is performed.^{13,45}

Bilateral vs Unilateral ILND in the cN0 PNC Patient. Kroon et al studied the lymphatic drainage in PNC patients using lymphoscintigraphy. In 20 patients studied, 18 (90%) patients demonstrated bilateral ILN drainage and in 1 (5%) patient drainage to the prepubic area were noted.⁴⁶ Therefore, bilateral ILND is always recommended. Similarly in patients in whom one groin is demonstrating an enlarged ILN while the other groin is cN0, the risk of harboring micrometastasis could be as high as 30% and

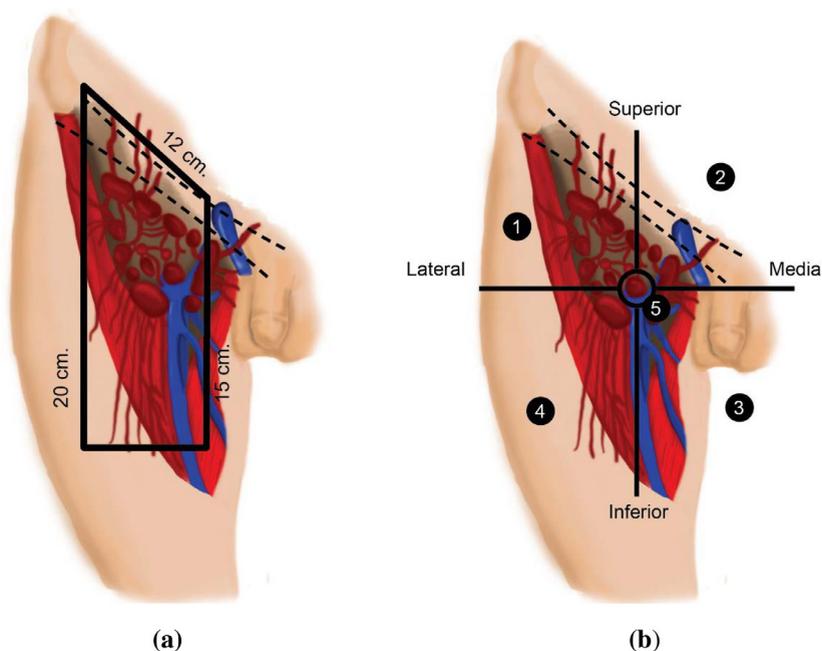
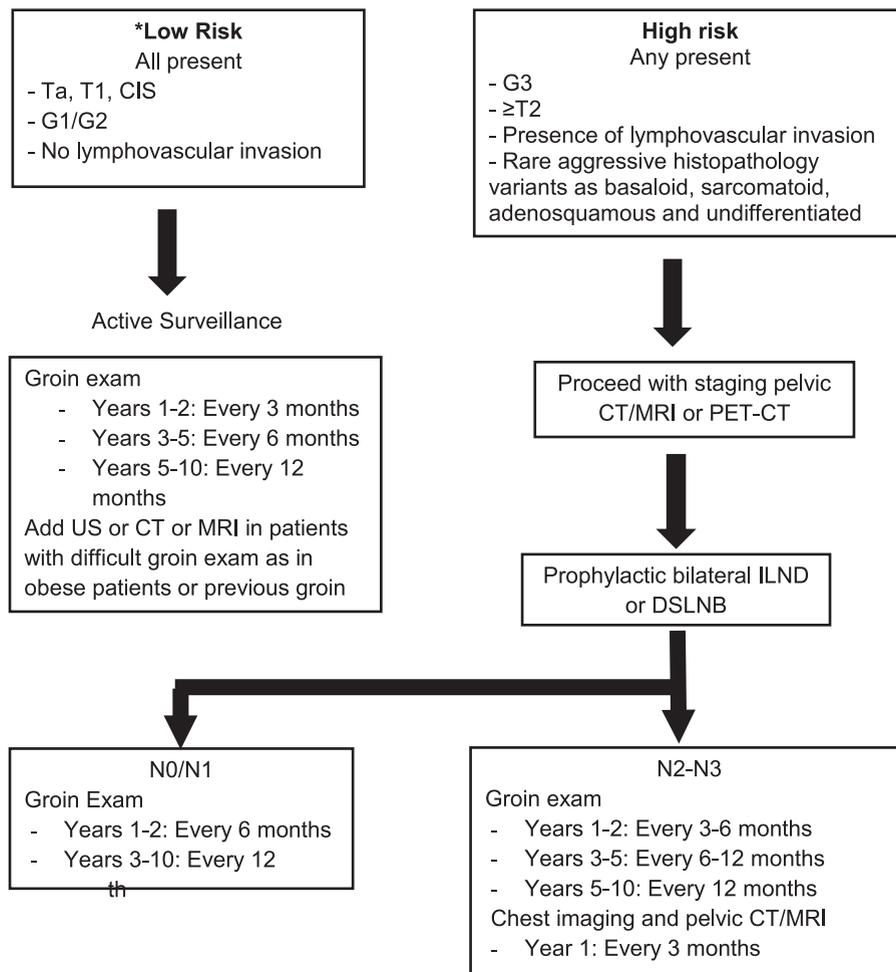


Figure 1. (a) Superficial inguinal lymph nodes boundaries as described by Daseler. (b) Zonal anatomy of the superficial inguinal lymph nodes as described by Daseler. (Color version available online.)



*T1G2 without LVI consider DSLNB or bilateral superficial ILND with intraoperative frozen section versus active surveillance

Figure 2. Proposed management algorithm for the cN0 PNC patient.

bilateral ILND is recommended.⁴⁷ In patients with cN0 and were placed on active surveillance and developed delayed ILN+ (>1 year from diagnosis); unilateral ILND is sufficient. Concomitant pelvic LND is indicated if the frozen section exam showed ≥ 2 positive ILNs.⁴⁸

Role of Prophylactic ILN Radiation Therapy in cN0 PNC Patient

Radiation therapy for the cN0 PNC patient has not been evaluated in a rigorous manner in the contemporary peer-reviewed literature. Arguments against prophylactic ILN radiation are the unproven efficacy, severe toxicity with potential crippling lower limb lymphedema, and the fibrotic changes that might hinder reliable follow-up with physical exam. Consequently, prophylactic ILN radiation to the patient with cN0 is not indicated.^{10,13}

Special Histological Considerations

Guimaraes et al studied the risk of ILN+ in 333 patients from Brazil. In those patients who developed ILN+ (overall 24%) such incidence classified by histological type was for, common squamous cell carcinoma type 28%, verrucous type 0%, warty type 17%, papillary type 12%, basaloid type 50%, sarcomatoid

type 75%, and adenosquamous type 50%.⁴⁹ Consequently; patients with PNC are classified into 3 risk groups for ILN+ based on PNC histologic type¹⁰

- 1) Low risk group: This includes verrucous, warty, and papillary types. Prophylactic ILND is not indicated as the risk of ILN+ is minimal.
- 2) Intermediate risk group: This includes the common squamous cell carcinoma and mixed forms. Prophylactic ILND is indicated based on pathological risk factors.
- 3) High-risk group: This includes the basaloid, sarcomatoid, adenosquamous, and poorly differentiated/undifferentiated types. Prophylactic ILND is indicated because of the high-risk of ILN+.

Follow-up Protocols Following Treatments in the cN0 PNC Patient

The follow-up for patients with cN0 will depend on the (1) choice of treatment of the groin (active surveillance/ILND) and (2) the pathological findings in patients who had an ILND¹³ and are detailed in Figure 2.

SUMMARY AND CONCLUSION

Management of the groin in the cN0 PNC patient represents a challenge to the treating urologic oncologist. Physical exam has limitations in detecting enlarged ILN in a subset of PNC patients. Tumor markers role is still evolving. Nomograms are not popular for use in the cN0 patients and are not externally validated. Overall imaging modalities are not sensitive or specific enough to rely on it as a sole investigation to rule out ILN+. DSLNB, in experienced centers, is more reliable than SSLNB in detecting micrometastasis. Pathological criteria in the primary tumor still will determine if a cN0 patient is to be offered active surveillance or prophylactic ILND. The adverse pathological features include the presence of G3 disease (>50% of tumor), stage \geq T2, LVI, and the rare histopathological variants; all warrant prophylactic ILND which should be performed bilateral. A limitation to our review is the lack of quality evidence; this is related to the rarity of the disease that poses challenges on conducting randomized prospective controlled trials testing new diagnostic and treatment modalities, similar to other more common genitourinary cancers. We illustrate a proposed algorithm for the management of the patient with cN0 based on the best available evidence in [Figure 2](#).

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2019.05.005>.

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