EVALUATION AND TREATMENT OF REGIONAL LYMPH NODES IN PENILE CARCINOMA

LEE SAY BOB
15/02/2015
## N STAGING (2010 TNM)

### N - Regional Lymph Nodes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>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>
</tbody>
</table>

### pN - Regional Lymph Nodes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pNX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>pN1</td>
<td>Intranodal metastasis in a single inguinal lymph node</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastasis in multiple or bilateral inguinal lymph nodes</td>
</tr>
<tr>
<td>pN3</td>
<td>Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of any regional lymph node metastasis</td>
</tr>
</tbody>
</table>
EVALUATION

• Careful palpation of both groins for the detection of enlarged inguinal LNs
  • Non palpable
  • Palpable
  • Fixity
ANATOMY OF INGUINAL NODES

Path for lymph flow from:
- glans penis (A)
- spongy urethra (B)
- skin of body of penis/scrotum (C)
- testis (D)

Lymph nodes:
- Lumbar
- Common iliac
- Internal iliac
- External iliac
- Superficial inguinal
- Deep inguinal
NON-PALPABLE INGUINAL NODES

• Micro-metastatic disease ~ 25%
• Current imaging techniques NOT reliable in detecting micro-metastases (EAU 2014)
  • Inguinal ultrasound (7.5 MHz) can reveal abnormal nodes with some enlargement
  • Conventional CT or MRI scans similarly cannot detect micrometastases reliably
  • 18FDG-PET/CT imaging does not detect LN metastases <10 mm
NON-PALPABLE INGUINAL NODES

• Exception (imaging)
  • obese patient
• Invasive LN staging is required in patients at intermediate- or high risk of lymphatic spread
PALPABLE INGUINAL NODES

• Highly suspicious for LN metastases
• P/E
  • number of palpable nodes on each
  • fixed or mobile
• Additional inguinal imaging does not alter management and is usually not required (EAU 2014)
PALPABLE INGUINAL NODES

- A pelvic CT scan can be performed in order to assess the pelvic LN
- 18FDG-PET/CT*
  - sensitivity of 88-100%
  - specificity of 98-100% for confirming metastatic nodes

MANAGEMENT OF REGIONAL LYMPH NODES

- Lymphatic metastases follows some anatomic rules
- The inguinal and the pelvic LNs are the regional drainage system
- The superficial and deep inguinal LNs
  - the first regional nodal group reached by lymphatic metastatic spread
MANAGEMENT OF REGIONAL LYMPH NODES

- Spread to the inguinal LN can be uni- or bilateral from any primary.

- A single photon emission CT (SPECT) study reported that all inguinal sentinel nodes were located in the superior and central inguinal zones, with most found in the medial superior zone.

- No lymphatic drainage to the two inferior regions of the groin, and no direct drainage to the pelvic nodes.


<table>
<thead>
<tr>
<th>Drainage zone</th>
<th>Location of sentinel nodes (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial superior zone</td>
<td>84 (73%)</td>
</tr>
<tr>
<td>Lateral superior zone</td>
<td>10 (8.7%)</td>
</tr>
<tr>
<td>Central zone</td>
<td>21 (18.3%)</td>
</tr>
<tr>
<td>Medial inferior zone</td>
<td>0</td>
</tr>
<tr>
<td>Lateral inferior zone</td>
<td>0</td>
</tr>
<tr>
<td>External iliac/obturator zone</td>
<td>0</td>
</tr>
<tr>
<td>Common iliac zone</td>
<td>0</td>
</tr>
<tr>
<td>Paraaortal zone</td>
<td>0</td>
</tr>
</tbody>
</table>
MANAGEMENT OF REGIONAL LYMPH NODES

- Second regional LN groups
  - ipsilateral pelvic lymph nodes

- Pelvic nodal disease does not seem to occur without ipsilateral inguinal LN mets

- Further mets LN spread from the pelvic nodes to paraaortic and paracaval nodes is outside the regional LN drainage system (sys mets ds)
Risk stratification depends on:
- stage
- grade
- the presence / absence of LVI in the 1° tumour

Tumours with low risk of mets ds are those with superficial (pTa, pTis) and low grade

pT1 tumours represent a heterogeneous risk group:
- pT1G1 low-risk
- pT1G2 intermediate-risk
- pT1G3 high risk

cN0

Surveillance vs Invasive nodal staging
cN0- SURVEILLANCE

- Patient survival is
  - > 90% with early lymphadenectomy and
  - <40% with lymphadenectomy for regional recurrence later

--- definite risk must be taken into account &
--- pt should be informed

- pTis and pTa, and with the appropriate caveats in pT1G1 tumours (EAU 2014)

- Prerequisite
  - good patient information and compliance
cN0- INVASIVE NODAL STAGING

• Staging in cN0 requires an invasive procedure since all imaging techniques are unreliable

• **FNAC** does not reliably exclude micrometastatic disease (low specificity) and is not recommended (EAU 2014)

== >> the pathological risk factors have to be used to stratify cN0 pts
APPROACH
(INVASIVE NODAL STAGING)

• 2 invasive diagnostic procedures (standard approaches) whose efficacy is evidence-based:
  • modified inguinal lymphadenectomy (mILNB) and
  • dynamic sentinel-node biopsy (DSNB)
mILND

- Modified inguinal lymphadenectomy (mILND)
  - standard surgical approach
  - defines a limited template whereby the superficial inguinal lymph nodes from at least the central and both superior Daseler’s zones are removed bilaterally and the greater saphenous vein is left in place


Fig. 1 – Division of the inguinal region into 5 zones according to Daseler.
Figure 1. Anatomical limits of MIL (1) and RIL (2)
DSNB

- DSNB is a tech based on the assumption that $1^\circ$ lymphatic drainage from a penile cancer goes to only 1 inguinal LN on each side which may however be in different locations based on individual anatomy.

Sentinel node concept

- Metastatic spread not a random process
- Sequential, stepwise spread
- Follows well known anatomic pathways
- Absence of metastasis in the sentinel node indicative of absence in the lymphatic drainage basin
DSNB - TECHNIQUE

- Tc99m nanocolloid is injected around the penile cancer site the day before surgery & additionally, patent blue can be injected before surgery.

- γ-ray detection probe is used intraop for the detection of the sentinel node which is possible in 97% of cases.
Dynamic Sentinel Node

Day of surgery

Gamma detector

Patent blue
Dynamic Sentinel Node
The protocol has been standardized for routine use and the learning curve is relatively short*

High sensitivity 90-94%*

In a pooled meta-analysis of 18 studies the pooled sensitivity was 88% and was improved to 90% with the additional use of patent blue#


Accuracy of Sentinel Lymph Node Biopsy for Inguinal Lymph Node Staging of Penile Squamous Cell Carcinoma: Systematic Review and Meta-Analysis of the Literature

Ramin S. Manshadi, MD, PhD, FACS
Vahid R. Amin, MD, PhD, FACS
From the Nephrology and Urology Research Center, Tehran University of Medical Sciences, Tehran, Iran. The Netherlands Cancer Institute, Amsterdam, The Netherlands

Purpose: Sentinel lymph node biopsy is emerging as a promising method for inguinal lymph node staging of penile squamous cell carcinoma. In the current systematic review we evaluated the accuracy of sentinel lymph node biopsy for inguinal lymph node staging of penile squamous cell carcinoma and studied possible influential factors.

Materials and Methods: MEDLINE®, Scopus®, ISI®, Ovid SP®, Springer, ScienceDirect® and Google™ Scholar were searched by the key words “(penile OR penis) AND sentinel”. No date or language limitation was imposed on the search and meeting abstracts were not excluded from analysis. A random effects model was used for statistical pooling.

Results: A total of 17 studies suitable for meta-analysis were detected. Three articles had 2 different subgroups of patients and each subgroup was considered as a separate study. Overall 18 studies (including the subgroups) were used for detection rate meta-analysis and 19 for sensitivity meta-analysis. The pooled detection rate was 88.3% (95% CI 81.9–92.6). Pooled detection rate of 90.1% (95% CI 83.6–94.1) was calculated for the studies using blue dye and radiotracers. The pooled sensitivity was 88% (95% CI 83–92). The highest pooled sensitivity (92% [95% CI 86–96]) was in the studies using radiotracer and blue dye, and recruiting only cN0 cases.

Conclusions: Sentinel lymph node mapping in penile squamous cell carcinoma is a method with a high detection rate and sensitivity. Using radiotracer and blue dye for sentinel lymph node mapping and including only cN0 disease ensures the highest detection rate and sensitivity.
Dynamic sentinel lymph node biopsy as the new paradigm for the management of penile cancer

Lawrence L. Yeung, M.D., Steven B. Brandes, M.D.,*

Division of Urology, Washington University School of Medicine, St. Louis, MO 63110, USA

Abstract

Objectives: The management of patients with penile cancer who have high-risk features for micrometastasis with clinically negative inguinal lymph nodes is controversial. We describe the history of the sentinel lymph node biopsy and how it has evolved to become a useful adjunct in the management of penile cancer.

Materials and methods: Using a PubMed search, we identified the evidence relating to the management of the inguinal lymph nodes in penile cancer between 1977 and 2010.

Results: The concept of the sentinel lymph node (SLN) was first described in 1977 for penile carcinoma where lymphangiograms were performed via the dorsal lymphatics of the penis to locate the primary lymphatic drainage zone of the penis situated near the saphenofemoral junction. Then, in 1992, the lymphatic mapping concept was further advanced by performing intradermal injections of blue dye to directly visualize the lymphatic channels and SLN in the treatment of melanoma. In 1994, investigators from The Netherlands pioneered the use of dynamic sentinel lymph node biopsies (DSLNB) for penile cancer by combining the use of peri-lesional blue dye injection, lymphoscintigraphy, and other future modifications of the technique to achieve low false negative biopsy rates (4.8%) as well as much lower morbidity (5.7%), compared with the 30%–50% morbidity associated with a full inguinal node dissection.

Conclusion: DSLNB significantly decreases the morbidity associated with performing a standard or even modified inguinal lymph node dissection in patients with clinically negative inguinal lymph nodes. Performing DSLNB requires a multidisciplinary team of urologists, nuclear medicine radiologists, and pathologists working in cohesion to attain the best SLN detection rates with the lowest possible false-negative rates. © 2013 Elsevier Inc. All rights reserved.
Dynamic Sentinel Node Biopsy in Penile Carcinoma: Evaluation of 10 Years Experience

Bin K. Kroon, Simon Horenblas, Willem Meinhardt, Henk G. van der Poel, Axel Bex, Harm van Tinteren, Renato A. Valdés Olmos, Omgo E. Nieweg

University of Leuven, Department of Urology, Belgium

Accepted 24 November 2004
Available online 27 December 2004

Abstract

Purpose: The aim of this study was to evaluate the results of 10 years dynamic sentinel node biopsy experience in penile carcinoma at our institute.

 Patients and Methods: 140 patients with clinically node-negative groins were prospectively included. Lymphoscintigraphy was performed after injection of 99mTc-Techneum-nanocolloid around the primary tumour. The sentinel node was intraoperatively identified with the aid of patent blue dye and a gamma ray detection probe. Lymph node dissection was performed only if sentinel node metastasis was found. Median follow-up was 52 months (range 5–129).

 Results: Lymphoscintigraphy visualized at least 1 sentinel node in 138 patients. Sentinel node metastasis was found in 37 inguinal regions of 31 patients. The sentinel node was the only tumour-positive node in 78% (29/37) of the dissection specimens. Complications occurred in 8% (17/206) of the operated groins. False-negative results were encountered in 6 patients resulting in a false-negative rate of 16% (6/37 patients). 5-year disease-specific survival was 96% and 66% for patients with a tumour-negative sentinel node and tumour-positive sentinel node, respectively (p = 0.001).

 Conclusion: Dynamic sentinel node biopsy in penile carcinoma is of important diagnostic, prognostic, and therapeutic value at the cost of only minor morbidity.

© 2004 Elsevier B.V. All rights reserved.
Conclusions: The false-negative and complication rates of DSNB have decreased since the procedure was modified. The current procedure has false-negative and complication rates of 4.8% and 5.7%, respectively. DSNB has matured into a reliable and safe method for assessing status of lymph nodes in cN0 penile carcinoma patients.
Dynamic Sentinel Lymph Node Biopsy in Patients with Invasive Squamous Cell Carcinoma of the Penis: A Prospective Study of the Long-Term Outcome of 500 Inguinal Basins Assessed at a Single Institution

Results and limitations: Five hundred inguinal basins in 264 patients underwent USS with or without FNAC and DSNB. Seventy-three positive inguinal basins (14.6%) in 59 patients (22.3%) were identified. Four inguinal basins in four patients were confirmed false negative at 5, 8, 12, and 18 mo. Two inguinal basins had positive USS and FNAC and negative DSNB results. Sensitivity of DSNB with USS, with and without FNAC, per inguinal basin was 95% and per patient was 94%. Sensitivity of DSNB alone per inguinal basin and per patient was 92% and 91%, respectively. The DSNB morbidity rate was 7.6%.

Conclusions: DSNB in combination with USS has excellent performance characteristics to stage patients with cN0 SCCp, with a 5% false-negative rate per node basin and a 6% false-negative rate per patient.
**SUMMARY cN0**

<table>
<thead>
<tr>
<th>Regional lymph nodes</th>
<th>Management of regional lymph nodes is fundamental in the treatment of penile cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>No palpable inguinal nodes (cN0)</td>
<td>Tis, Ta G1, T1G1: surveillance</td>
</tr>
<tr>
<td></td>
<td>&gt; T1G2: invasive lymph node staging by bilateral modified inguinal lymphadenectomy or DSNB.</td>
</tr>
</tbody>
</table>
cN1/cN2

• Likelihood for metastatic LN disease is high

• No unnecessary delays (antibiotics)

• Appropriate oncological diagnosis & tx, should be undertaken before further mets spread

• In clinically doubtful cases, us-guided FNAC can be an option*

• Palpably enlarged inguinal LNs, additional staging ix are not useful

(EAU 2014)

cN1/cN2

- Imaging do not provide additional info about the inguinal LNs except in very obese patients

- However, CT or MRI can provide information about the pelvic nodal status

- 18F-FDG-PET/CT can identify additional metastases in LN positive patients

- DSNB is NOT reliable in patients with palpably enlarged and suspicious inguinal LNs and should not be used
RADICAL INGUINAL LYMPHADENECTOMY (LAD)

- Surgical staging by inguinal LAD

- Intraop frozen sections may be used to confirm LN mets in which case an ipsilateral radical LAD is required

- Radical inguinal LAD carries a significant morbidity related to problems of lymph drainage from the legs & wound healing

- Morbidity ~as high as 50% with ↑ BMI and Sartorius muscle transposition being significant risk factors for complications
RADICAL INGUINAL LYMPHADENECTOMY

• **Lymph-node density** is a prognostic factor

• The surgical technique
  • meticulous regarding tissue handling
  • ligation or possibly clips for lymphatics as the wall of lymphatic vessels does not contain smooth muscle

• Additional measures counteracting postoperative lymphatic stasis and leakage
  • stockings, bandaging of legs, inguinal pressure dressings, vacuum suction, prophylactic antibiotics
RADICAL INGUINAL LYMPHADENECTOMY

• In advanced cases, reconstructive surgery is often necessary for primary wound closure

• The most commonly reported complications in recent series were
  • wound infections (1.2-1.4%)
  • skin necrosis (0.6-4.7%)
  • lymphedema (5-13.9%)
  • lymphocele formation (2.1-4%)

PELVIC LYMPHADENECTOMY

• Patients with +ve pelvic nodes have a worse prognosis compared to pts with only inguinal nodal mets (5-year CSS 71.0% vs. 33.2%)*

• If ≥2 positive LNs or 1 node with extracapsular extension (pN3) are found on one side, an ipsilateral pelvic LAD is indicated

• No direct lymphatic drainage from penile tumours to the pelvic LNs
  • --- pelvic LAD is not indicated if there is no involvement of inguinal LNs on that side.

• Pelvic LAD may be performed simultaneously or as a 2° procedure following definitive histology

• If bilateral pelvic dissection is indicated, it can be performed through a midline suprapubic extraperitoneal incision

• Important to avoid unnecessary delay if these procedures are indicated
ADJUVANT TREATMENT

- In patients with pN2/pN3 disease, adjuvant chemo is recommended
  - long-term DFS 84% was reported for node +ve pts with adjuvant chemo after radical LN surgery compared to w/o chemo only 39%*

- Adjuvant radiotherapy has been used after inguinal LAD
  - published evidence very limited
  - not generally recommended
  - no reported results of adjuvant radio-chemotherapy

cN3

• The presence of mets ds in these cases is beyond doubt

• Additional diagnostic measures do not alter the immediate management
  • (staging by CT TAP is indicated in order to assess the presence of further pelvic LN ds and systemic mets)

• In clinically unequivocal cases, histological verification by biopsy is not required

• In rare cases with doubt, excisional or core needle biopsy may be done

(UEAU 2014)
cN3

- Upfront surgery is not generally recommended as
  - non-curative
  - quite destructive

- Multimodal tx with neoadjuvant chemo followed by radical LAD in clinically responsive cases is recommended
  - responders achieve long-term survival in 37% of cases

MANAGEMENT OF LYMPH NODE RECURRENCE

• Pts with regional recurrence after surveillance should be treated in the same way as pts with primary cN1/cN2 ds

• Pts with regional recurrence following -ve invasive staging by DSNB or mILB
  • have a disordered inguinal lymphatic drainage anatomy
  • must be considered at a high risk of irregular mets progression
MANAGEMENT OF LYMPH NODE RECURRENCE

• Pts with inguinal nodal recurrence after therapeutic radical inguinal LAD have been reported to have a 5-year CSS of 16% *

• There is no evidence for the best mx in such cases but multimodal treatment with neoadjuvant and/or adjuvant chemo after radical LN surgery is advised (EAU 2014)

THE ROLE OF RADIOTHERAPY FOR THE TREATMENT OF LN DISEASE

• Radiotherapy of LN disease in penile cancer is NOT generally recommended

• Prophylactic radiotherapy for cN0 disease is NOT indicated

• Adjuvant inguinal radiotherapy
  • may be considered as an option in selected patients with extracapsular nodal extension (cN3) or
  • as a palliative tx for surgically irresectable disease
### SUMMARY

<table>
<thead>
<tr>
<th>Regional lymph nodes</th>
<th>Management of regional lymph nodes is fundamental in the treatment of penile cancer</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No palpable inguinal nodes (cN0)</td>
<td>Tis, Ta G1, T1G1: surveillance. &gt; T1G2: invasive lymph node staging by bilateral modified inguinal lymphadenectomy or DSNB.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Palpable inguinal nodes (cN1/cN2)</td>
<td>Radical inguinal lymphadenectomy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed inguinal lymph nodes (cN3)</td>
<td>Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic lymphadenectomy</td>
<td>Ipsilateral pelvic lymphadenectomy is indicated if two or more inguinal nodes are involved on one side (pN2) and in extracapsular nodal metastasis (pN3).</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>Indicated in pN2/pN3 patients after radical lymphadenectomy</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Radiotherapy is not indicated for the treatment of nodal disease in penile cancer.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DSNB** = *dynamic sentinel node biopsy.*
CONCLUSION

- LAD remains as integral part of mx in penile cancer, most important prognostic factor
- Early LAD improves prognosis and survival
- Surveillance strategies recommended for well informed, low risk cN0 pt
- Multidisciplinary mx in penile cancer to optimize tx and improved survival