A novel technique for surgical nodal staging in penile cancer

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Management of Penile Cancer

• Management of the primary lesion
  • Penile preserving surgery
  • Amputations

• Management of the regional lymph nodes
  • Inguinal
    • Palpable nodes
    • Non-palpable nodes
  • Pelvic
Regional Lymph Nodes

“Pathological nodal staging is the singularly most important prognostic factor in penile cancer”

<table>
<thead>
<tr>
<th>N-stage</th>
<th>CSS 5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>pNO</td>
<td>85-94%</td>
</tr>
<tr>
<td>pN1</td>
<td>79-89%</td>
</tr>
<tr>
<td>pN2</td>
<td>7-60%</td>
</tr>
<tr>
<td>pN3</td>
<td>0-7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of involved nodes</th>
<th>CSS 5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>75%</td>
</tr>
<tr>
<td>4-5</td>
<td>8.4%</td>
</tr>
<tr>
<td>&gt;5</td>
<td>0</td>
</tr>
</tbody>
</table>

Regional Lymph Nodes

- SCC penis spreads in a predictable and stepwise manner:
  - Bilaterally to the inguinal nodes
  - Then to ipsilateral pelvic nodes or distant spread
- Distant metastases virtually is never seen without inguinal node involvement
Non-Palpable Nodes

- Clinically node negative patients have up to 20% occult metastases
- Non-invasive methods for assessing non-palpable groin nodes are unreliable
  - Clinical examination
  - Ultrasound
  - CT
  - MRI
- Surveillance
Non-Palpable Nodes

- Kroon et al: J Urol 2005
  - 20 patients Groin dissections following DSNB vs 20 patients Groin dissection after surveillance
  - 3 year survival 84% vs 35%

- Several studies have similarly shown this improved survival (Ravi 1993, Srinivas et al 1987, Fraley et al 1989)

Thus recommendation for prophylactic inguinal lymphadenectomy
Inguinal Lymphadectomy

Standard lymphadectomy boundaries:
- Inguinal ligament
- Sartorius
- Adductor Longus
- Apex femoral triangle

Significant Morbidity
- Wound Infection: 3-70%
- Necrosis: 2.5-64%
- Seroma: 5-84%
- Lymphoedema: 5-100%
Non-Palpable Nodes

• Risk Adapted Approach
  • Surgery in patients that need it
  • Avoid complications
  • Reduce false negative results
Predictors of Lymph nodes metastases

1. T stage (corpora cavernosa invasion)
2. Grade
3. Vascular/Lymphatic invasion
4. Growth Pattern

# Predictors of Lymph nodes metastases

## Penile Carcinoma
### Prognostic Factors for Inguinal Lymph Node Metastasis

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Tis</td>
<td>T1 G2*, T2 G 1-2,</td>
<td>Grade III Vascular Invasion</td>
</tr>
<tr>
<td>Criteria</td>
<td>Ta</td>
<td>No Vascular Invasion</td>
<td>T ≥ 2</td>
</tr>
<tr>
<td></td>
<td>T1 Grades 1</td>
<td>No Vascular Invasion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Vascular Invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Metastasis</td>
<td>&lt;10% ICUD(1)</td>
<td>10-50% ICUD(1)</td>
<td>&gt;50% ICUD(1)</td>
</tr>
<tr>
<td></td>
<td>&lt;16% EAU(2,3)</td>
<td>≥17% EAU(2,3)</td>
<td>68-73% EAU(2,3)</td>
</tr>
</tbody>
</table>

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1. ICUD: Initial Centre for Urological Data
2. EAU: European Association of Urology
3. SIU: Societe Internationale d’Urologie

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* T1G2—either low or intermediate risk in some series (refs 95, 104, 106)
Predictors of Lymph nodes metastases

- Hegarty et al, BJUI 2006

- Prospective study 100 cases managed according to EAU guidelines

- 33 men with cN0 had prophylactic node dissections as per EAU guidelines; 6 had positive nodal disease, 18%

- 82% therefore had unnecessary inguinal node dissections
Can we reduce morbidity of ILND?

- Modified lymphadenectomy – designed to remove nodes from the most probable location of first line invasion
- Daseler regions
Modified Inguinal Lymphadenectomy

Modified lymphadectomy to reduce morbidity of groin node dissection; Catalona 1988

Boundaries
- External oblique above Spermatic Cord
- Lateral border femoral artery
- Adductor Longus
- Lower end fossa ovalis
- Saphenous vein spared
## Modified Inguinal Lymphadenectomy

### Complications of Standard Inguinal Lymph (SIL) & Modified Inguinal Lymph (MIL)

<table>
<thead>
<tr>
<th>Ref</th>
<th>Period</th>
<th>No Lymphadenectomies</th>
<th>% Skin Edge Necrosis</th>
<th>% Lymphoedema</th>
<th>% Wound Infection</th>
<th>% Lymphocele</th>
<th>% Seroma, Lymphocele</th>
<th>% Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIL</td>
<td>1948 - 2003</td>
<td>780</td>
<td>51</td>
<td>31</td>
<td>16</td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MIL</td>
<td>1988 - 2001</td>
<td>136</td>
<td>4</td>
<td>18</td>
<td>7</td>
<td>14</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

High reports of false negative findings (up to 15%)
Dynamic Sentinel Node Biopsy

- Removing first sentinel node
- Base on anatomical landmarks
- Static

- Patent blue-V

- Addition of technetium-99m-labelled nanocolloid
  - Sensitivity 80%

- Addition of ultrasound +/-FNA,
  - Intraoperation palpation
  - Change in pathological examination to serial sectioning and immunohistochemistry
  - Sensitivity 93-95%, specificity 100%

Dynamic Sentinel Node Biopsy

- Saves up to 70% of prophylactic node dissections
- Does not compromise treatment
- Reduces morbidity
- False neg rates have fallen from 22% to 4.8% with pre-operative US FNAC

Dynamic Sentinel Node Biopsy

2-day protocol

Injection of 40MBq Tc99m in three sites along the penile shaft circumference distally (2, 6, 10 position after o’clock)

Following lymphoscintigraphy the SNs are marked on the patient’s skin

1-day protocol

Injection of 20MBq Tc99m in three sites along the penile shaft circumference distally (2, 6, 10 position after o’clock)

Following lymphoscintigraphy the SNs are marked on the patient’s skin

Intraoperatively 0.3-0.5 mL of patent blue are injected distally in three different sites along the penile shaft circumference (2, 6, 10 position after o’clock)

Following an inguinal incision, nodes that are radioactive (using the gamma-probe) ± blue or abnormally palpable are removed.

Patient goes home on the same day of the procedure
Dynamic Sentinel Node Biopsy
## DSNB Complications

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>necrosis</th>
<th>oedema</th>
<th>Infection</th>
<th>seroma</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSNB</td>
<td>&gt;1000</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

Sentipen Trial

- First feasibility study investigating use of Sienna in nodal staging for penile cancer
- 10 patients recruited who were due to undergo standard DSNB
- Underwent standard Ultrasound +/- FNAC followed by radioactive nanocolloid dynamic sentinel node biopsy protocol
- Concurrent subcutaneous injection of 2ml of Sienna in 4 divided doses peritumoral or distal penile shaft
- Sentinel nodes were retrieved using the Sentimag probe in conjunction with the gamma probe
Sentipen Trial
Sentipen Trial
Sentipen Trial

- Mean age 67.6 (48-83)
- Mean BMI 28.6
- Primary tumour:
  - 3 x G3pT1
  - 1 x G2pT2
  - 4 x G3pT2
  - 2 x G3pT3
- Mean time from primary surgery to DSNB – 71 days
- All patients had U/S +/- FNAC and nanocolloid protocol DSNB
- 9 patients underwent Sentimag assisted node biopsy; 1 patient excluded due to mechanical failure of the Sentimag probe
Sentipen Trial

- Mean time from nanocolloid injection to surgery: 20.2h (7.75 - 25.7)
- Mean time from Sienna injection to surgery: 14.1h (1.17 - 21.3)
- Mean surgery time: 84.4 minutes (70 – 120)

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sienna</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Concordance of 90% (Cohen’s Kappa)

- 3 positive nodes were retrieved – all detected with both techniques
Sentipen Trial

• We conclude that the use of Sienna+ (now Magtrace) and the Sentimag probe is a safe and effective method to detect sentinel nodes in patients with squamous cell carcinoma of the penis.
• It has the potential to be a more efficient method than present techniques.
• It may be more easily adopted as it does not require a nuclear medicine department
• Further studies are in progress