MANAGEMENT OF PENILE CANCER

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PGY-5
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Outline

- Focal Therapy
- Mx of nonpalpable nodes
- Mx of palpable nodes
Natural History

- Stepwise progression:
  - Penis → Inguinal → Pelvic nodes → Mets
- No Skip lesions, no mets with LN -ve
- Overall 5 yr Cancer specific survival approx 50%
- Most untreated patients die within 2 years

Broder Grading System

A Key Prognosticator:

Grade 1: Low grade, ‘well differentiated’
Grade 2: Intermediate, ‘moderately differentiated’
Grade 3, 4: High grade, ‘poorly differentiated’
<table>
<thead>
<tr>
<th>Stage</th>
<th>Sixth Edition</th>
<th>Seventh Edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Primary tumor cannot be assessed</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades the adjacent tissues</td>
<td>Tumor invades superficial connective tissue without lymphovascular invasion and is not poorly differentiated</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades the adjacent tissues and is poorly differentiated</td>
<td>Tumor invades superficial connective tissue with lymphovascular invasion and is poorly differentiated</td>
</tr>
</tbody>
</table>

**Regional Lymph Nodes:**
- N0: No regional lymph node metastases
- N1: Metastasis to a single regional lymph node
- N2: Metastasis to multiple regional lymph nodes
- N3: Metastasis to a combination of deep pelvic lymph nodes and a single inguinal lymph node

**Clinical Staging:**
- M0: No distant metastases
- M1: Distant metastases
Predicting Survival

- Presence of + LNs
- Number of + LNs
- Bilateral nodes
- Pelvic nodes
- Extranodal extension

- Survival depends on the lymph nodes!

Predicting LN Metastasis

- T Stage
  - T3: 78% LN +
  - T1 low grade: 4% LN +
- Grade
  - Well diff: 30% LN involvement
  - Mod-poor: 81% LN involvement
- Lymphovascular invasion
- Histology
  - Verrucous: No mets
  - Basaloid: Highest risk
- Size
- Location (prox, distal)
- Molecular markers (p53, etc)
Case: 56 yr man presents with erythematous plaque on penis

Penile CIS

- Treatment is conservative (Options)
  - Topical 5FU, Imiquimod
  - Laser
  - Moh’s Surgery
  - Brachy/XRT
  - Organ sparing surgery

Only 10% of CIS progress to invasive SCC
Nd:YAG laser

- Technique:
  - PDD (Photodynamic diagnosis) with Nd:YAG laser tx
  - Apply Lidocaine jelly and 5-ALA to the penis
  - 5-ALA selectively accumulates in tumor cells and metabolizes to fluorescent protoporphorin

- Laser Ablation
  - 5-10mm distance from tissue, Margin of 3mm coagulated

- Quality Control
  - Biopsy of tumor base
  - Reexamine under fluorescent light

- Schlenker et al., 2009

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LASER Studies comparison

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Laser</th>
<th>Mean follow-up (months)</th>
<th>Recurrence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mullay et al. (1988)</td>
<td>15</td>
<td>Nd:YAG</td>
<td>28</td>
<td>31.2%</td>
</tr>
<tr>
<td>Bandiera et al. (1988)</td>
<td>10</td>
<td>CO₂</td>
<td>7</td>
<td>9.5%</td>
</tr>
<tr>
<td>Taeijen and Malek (1988)</td>
<td>44</td>
<td>CO₂, Nd:YAG, KTP-532</td>
<td>58</td>
<td>11.4%</td>
</tr>
<tr>
<td>van Beuzijen et al. (2001)</td>
<td>19</td>
<td>CO₂, Nd:YAG</td>
<td>32</td>
<td>26%</td>
</tr>
<tr>
<td>Finneberger et al. (2002)</td>
<td>29</td>
<td>Nd:YAG</td>
<td>46.7</td>
<td>6.8%</td>
</tr>
<tr>
<td>Windahl and Anderson (2003)</td>
<td>67</td>
<td>CO₂ and Nd:YAG</td>
<td>60</td>
<td>19%</td>
</tr>
<tr>
<td>Meijer et al. (2007)</td>
<td>44</td>
<td>Nd:YAG</td>
<td>Not reported</td>
<td>48%</td>
</tr>
</tbody>
</table>

Abbreviations: CO₂, carbon dioxide; KTP, potassium titanyl phosphate; Nd:YAG, neodymium-doped yttrium aluminum garnet.

Antunes et al., 2007
Conclusions about Lasers

- Variable success rates
  - No RCTs comparing lasers or techniques
- Stage dependant
  - Good results for Tis tumors (local recurrence 0-10%)
  - Mixed results for T1 (local recurrence 25%)
  - Avoid in T2 tumors
- Good functional Results
  - 75% stable erectile function, 75% resume normal sexual activity
  - Windahl et al., 2004

Moh’s Surgery Outcomes

- N= 41, Tis-T2
- Local control: 68% at mean 5 yr followup
  - 30% recurrence SCCA
  - 21% recurrence Tis

- Shindel et al., 2007
Organ preserving surgery

Table 1 Recurrence rates among patients who underwent conservative surgery.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Mean follow-up (months)</th>
<th>Recurrence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derniak (1999)¹³</td>
<td>64</td>
<td>60</td>
<td>12%</td>
</tr>
<tr>
<td>Biasada et al. (2003)¹¹</td>
<td>30</td>
<td>180</td>
<td>30%</td>
</tr>
<tr>
<td>Pietrzak et al. (2004)¹²</td>
<td>32</td>
<td>16</td>
<td>3.1%</td>
</tr>
<tr>
<td>McDougal (2005)²¹</td>
<td>7</td>
<td>36</td>
<td>14.2%</td>
</tr>
</tbody>
</table>

*Only K0 patients were included.

Case: 62 yr man, biopsy T1G3 SCC. Nonpalpable lymph nodes
Question

- How should this T1G3 tumor be treated?
  - 5FU
  - Laser
  - Brachy
  - Glansectomy/Organ preserving surgery
  - Partial Penectomy

Rationale for Organ Preserving Treatment

- Traditional 2 cm margin may be excessive
- Significant psychosocial effects of traditional partial/total penectomy
- Higher local recurrence rates can be salvaged with surgery.
2 cm margin unnecessary?

- 80% of all tumors have <5mm microscopic extension beyond visible tumor edge
  
  *Agarwal et al., 2000*

<table>
<thead>
<tr>
<th>Grade</th>
<th>N</th>
<th>S</th>
<th>T0</th>
<th>T5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>2</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>5*</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>2</td>
<td>3</td>
<td>Nil</td>
</tr>
</tbody>
</table>

*One of these showed only dysplasia.

© 2000 BJU International 85, 299-301

- Several case series demonstrating good local control with <2cm margins
- 51 pts undergoing organ preserving surgery
  - <10mm margin in 48%, <20mm margin in 90%
  - Local recurrence in 2/51

*Minhas et al., 2005*
Psychological effects

Challenges of Organ Sparing Treatments
- Risk of understaging
- Unknown post-treatment margin status
- Rare Disease
  - No RCTs to adequately compare treatment modalities
Indications for organ-sparing treatments

- **Ta, Tis, T1 grade 1-2** (Campbell’s)
- **T1G3, T2G1/2 if:** (EAU guidelines)
  - Lesion takes up <50% of glans
  - Reliable f/u ensured

**Case: T1G3, nonpalpable Lymph Nodes**

- What further investigations are required?
  - CT abdo/pelvis
  - Liver enzymes
  - CXR
  - Bone Scan
Question:

- T1G3 with nonpalpable nodes (primary treated with glansectomy). What is the next step in the management of this patient?
  - Followup with serial physical exams
  - Bilateral dynamic sentinel node biopsy
  - Bilateral modified inguinal node dissection
  - Bilateral radical inguinal node dissection

Clinical Status of Nodes NOT reflective of pathological status

- Of Patients presenting with Palpable Nodes
  - 50-60% are cancer
- Of Patients presenting with Nonpalpable Nodes
  - 20-30% have micromets

Heyns et al., 2010
Reasons for Aggressive Prophylactic LND

1) Morbidity has lessened
   - Historical Complication rates 80% --> 30-70% in contemporary series

2) Patients with Micromets (NONPALPABLE nodes) have the greatest benefit from LND because they can be CURED

- 5 year disease specific survival rates
  - Pts undergoing LND for nonpalpable +ve nodes: 84%
  - Pts undergoing LND for palpable disease: 33%  
    
McDougal, 1995
Reasons for Aggressive Prophylactic LND

3) Delayed LND can rarely salvage patients who develop delayed lymphadenopathy

- 3 yr Disease specific survival
  - Early LND that was pN+: 85%
  - Delayed LND for recurrence: 35%

Kroon et al., 2005

Predicting LN metastasis

Ficarra et al., 2006
Predicting LN metastasis

- 4 Variables: STAGE, GRADE, Vascular invasion, Histology

- CIS: Only 2 cases reports of LN+
- Verrucous Ca (Ta): NO cases of LN+
- T1G1: <10% incidence of LN+
- T1G2: Controversial
- T1G3 or Vascular invasion: up to 50%
- T2: 60%  
  
Margulis et al., 2010

T1 G2 risk of LN metastasis

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of G2T1 patients</th>
<th>No. with positive nodes</th>
<th>Percentage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDougal [10]</td>
<td>24</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Solsona et al [11]</td>
<td>23</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Hungerhuber et al [12]</td>
<td>13</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Hegarty et al [3]</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Novara et al [13]</td>
<td>23</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>Naumann et al [4]</td>
<td>20</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>
Recommended LN Management

- T1G1, CIS: Watchful waiting
- T1G2: Controversial, most NA practitioners do not do LN Dissection
- T1G3, ANY T2: Must interrogate the LNs

Options for LN sampling (Nonpalpable nodes)

- Dynamic Sentinel Node biopsy
- Modified LN dissection
- Radical LN dissection
Inguinal LN drainage

- Key Points
  - Cancer progresses superficial to deep
    - no skip lesions
  - Penis drains BILATERALLY to Inguinal lymphatics in 80% of cases
Dynamic Sentinel Node Biopsy

- Technique (2 combined methods of SN location)
  1) PREOP: Technetium-99m nanocolloid injected at tumor site --> Dynamic anterior lymphoscitigraphy.
  2) INTRAOP: Patent blue dye injected around tumor 1 hr prior to surgery. Gamma detector intraop.

Outcomes of DSLN biopsy

- Study of 50 cases: ALL within central and superomedial zone
  - False negatives 20 → 4% (Netherlands)
  - Requires center of expertise (>20 cases/year)
  \[\text{Leitje et al., 2007}\]

- However, other series have shown False negative rates as high as 50%
Case: T1G3 primary, Nonpalpable Lymph Nodes

- What is the next step in the management of this patient?
  - Followup with serial physical exams
  - **Bilateral sentinel node biopsy**
  - **Bilateral modified inguinal node dissection**
    - Bilateral radical inguinal node dissection

Case 3

- T2G3 tumor treated with partial penectomy. Palpable L inguinal nodes. The next step in treatment of this patient would be:
  - Antibiotics x 6 weeks. LND if lymphadenopathy persists
  - Immediate modified LND
  - Immediate radical LND
  - Fine Needle aspiration of Lymph Node
The role of Antibiotics

- Even if nodes decrease in size with Antibiotics, pt may still have mets
- Delayed LND reduces survival
  
  Leijte et al., 2007

Question:

- This patient with T2G3 SCC requires immediate LN sampling. What would be your initial approach?
  - L dynamic sentinel node biopsy
  - L Radical Node dissection
  - L Radical Node dissection + R modified Node dissection
  - Bilateral Modified Node dissection
  - Bilateral Radical Node dissection
  - L US guided Biopsy of Node
Management of T2G3 with Palpable Left Nodes

- **Ipsilateral Side:**
  - Modified LND
  - Direct to Radical NODE dissection: Tx of Choice in most centers (EAU guidelines)
- **Contralateral Side:** (CONTROVERSIAL):
  - Hegarty, EAU guidelines: prefer Modified LND

Pelvic Lymph Node Dissection

- Pelvic LN status predicted by Inguinal Nodes:
  - 1 inguinal node +ve: <5% pelvic LN +ve
  - 2-3 inguinal node +ve: 23% Pelvic LN +ve
  - 4+ node +ve: 56% pelvic LN +ve
- Indication for Pelvic LND is controversial:
  - 2 or more Inguinal node +ve (EAU guidelines)
Benefits of Pelvic Lymph Node dissection

- Disease Staging
  - Prognosis
  - Determine candidacy for adjuvant chemo
- Possible curative advantage
- Little additional morbidity

Summary

- Organ Preserving surgery:
  - Allows better preservation of sexual function
  - Higher rates local recurrence than partial/total penectomy
  - Salvage surgery appears to be successful in disease control
Summary

- Management of NONPALPABLE Nodes:
  - T1G1/2, Tis, Ta: Active Surveillance
  - ANY T2+, ANY G3+, Vascular invasion, Basaloid subtype: Bilateral Modified LND or Bilateral DSNB

Summary

- Management of PALPABLE Nodes:
  - Low risk: Consider 4-6 week antibiotic trial. LND if persistent
  - High risk: Immediate Bilateral LND
  - Ipsilateral Pelvic LND if 2+ inguinal nodes
Acknowledgement

- Dr. Black

And now for a dose of radiation...
Delayed Palpable LNs after period of surveillance

- Traditionally required Unilateral LND
- Risk of Contralateral Occult Metastasis:
  - 10% risk overall
  - 30% risk IF >2 LN on ipsilateral side
  - HORENBLAS et al., - ref 64 of Hegatry et al

- EAU Guidelines:
  - Unilateral radical LND
    - >6 mos disease free (definition of ‘delayed’)
    - <3 LN positive on other side.
  - Bilateral radical LND
    - < 6 mos disease free
    - >2 LN positive on Unilateral side
Modified LND

- Modified does not equate to ‘superficial.’

Sample nodes in fossa ovalis MEDIAL to femoral vein

- False Negative up to 5%

Radical LND

- Wider area of dissection
- Deep to fascia lata
- Skeletonize femoral vessels
- Require sartorius flap over vessels
CASE: T2 Penile Ca and PALPABLE Lymph Nodes

- How would you manage the primary lesion?
  - Partial Penectomy
  - Total Penectomy with perineal urethrostomy
  - Brachytherapy
  - Penile Preserving Surgery

Partial Penectomy

- Outcomes of Partial
  - 0-7% rate of local recurrence
  - 20% men report adequate sexual function