Sentinel Lymph Node Mapping and Ultrastaging in Vulvar Carcinoma

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Vulvar Squamous Cell Carcinoma

• 56 year old woman
• Long-standing vulvar pruritus
• Notes growing mass at introitus
• Partial radical vulvectomy with sentinel lymph node biopsy
Sentinel Nodes are Medial
Sentinel lymph node, frozen section

Sentinel lymph node, permanent section

Sentinel lymph node, level 1 of ultrastaging protocol
Incidence of Vulvar Malignancies

- Uterus: 54%
- Ovary: 26%
- Cervix: 14%
- Vagina: 6%
- Vulva: 6%
- Squamous Cell Ca: 90%
- Melanoma: 5-10%
- Other: 1-5%
Morbidity of Inguinofemoral Lymph Node Dissection

- Nodal status most important prognostic factor
- 20-30% clinically negative LNs have metastases
- Prognostic information obtained with high potential for morbidity in 70-80%
  - 14-48% lymphedema
  - 7-40% lymphocele
  - 21-39% wound breakdown

Image courtesy of Dr. Charles Levenback
Historical Attempts to Reduce Morbidity

• 1979 DiSaia: inguinal lymph nodes above cribiform fascia, “sentinel”
  – With (-) inguinal LN, risk of (+) pelvic or femoral LN low
• GOG-74 (Stehman, et al 1992)
  – 121 pts: ipsilateral superficial inguinal lymphadenectomy
  – Fewer complications compared to radical surgery
  – 7.3% groin recurrence (0% in historical controls)
Modern Sentinel Lymph Node Concept

Injection of blue dye or radiocolloid around tumor

Primary tumor

Sentinel lymph node

Sentinel node first site of metastasis

Regional nodes
Intraoperative Lymphatic Mapping for Vulvar Cancer

CHARLES LEVENBACK, MD, THOMAS W. BURKE, MD,
DAVID M. GERSHENSON, MD, MITCHELL MORRIS, MD, ANAIS MALPICA, MD,
AND MERRICK I. ROSS, MD

- Superficial site, ease of injection
- Fairly predictable lymphatic drainage
- Mapping allows detection of aberrant drainage to deep LNs
- Feasibility study of 9 patients (12 groins)
Sentinel Lymph Nodes and Vulvar Carcinoma

- Most studies identified SLN in >90% of pts
- False negative rate 0-8.3%
- Groin recurrence 2.3% in 259 pts with SLN alone
- False negative associated with:
  - Inexperienced
  - Tumor size >4.0 cm
  - Midline tumors
  - Clinically positive lymph nodes
Value of Ultrastaging

- Fewer LNs received allows for more thorough, targeted examination than would be practical in a standard dissection
- 4-23% increase in detection over standard processing
- 58% smaller metastases detected
### Variability in Ultrastaging Protocols

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th># Patients</th>
<th>Ultrastaging Protocol*</th>
<th>False Negative</th>
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<tbody>
<tr>
<td>de Hullu</td>
<td>2000</td>
<td>26</td>
<td>3 H&amp;E/mm + pankreatin if H&amp;E (-)</td>
<td>0</td>
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<tr>
<td>de Cicco</td>
<td>2000</td>
<td>37</td>
<td>3 H&amp;E’s 0.3 to 1.0 mm into block</td>
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<tr>
<td>Sliutz</td>
<td>2002</td>
<td>26</td>
<td>Block cut through 400µm intervals H&amp;E + unstained; pankreatin if H&amp;E (-)</td>
<td>0</td>
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<tr>
<td>Moore</td>
<td>2003</td>
<td>29</td>
<td>5 H&amp;E’s at 100µm intervals</td>
<td>0</td>
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<tr>
<td>Puig-Tintore</td>
<td>2003</td>
<td>26</td>
<td>2 H&amp;E’s + unstained 400µm intervals ; CKC if H&amp;E (-)</td>
<td>0</td>
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<tr>
<td>Martinez-Palones</td>
<td>2006</td>
<td>27</td>
<td>IHC for pankreatin if initial H&amp;E negative</td>
<td>1/27</td>
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<tr>
<td>Rob</td>
<td>2007</td>
<td>59</td>
<td>Serial sections 40µm intervals (every 3rd slide CKC)</td>
<td>0</td>
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<tr>
<td>Vidal-Sicart</td>
<td>2007</td>
<td>70</td>
<td>1H&amp;E + 1 pankreatin 400µm into block</td>
<td>0</td>
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<tr>
<td>Hampl</td>
<td>2008</td>
<td>127</td>
<td>Block cut through at 200µm intervals H&amp;Es + unstained for pankreatin</td>
<td>3/127</td>
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<tr>
<td>Van der Zee</td>
<td>2008</td>
<td>457</td>
<td>3 H&amp;E/mm + pankreatin if H&amp;E (-)</td>
<td>N/A</td>
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<tr>
<td>Achimus-Cadariu</td>
<td>2009</td>
<td>59</td>
<td>Block cut through at 200µm intervals for maximum of 6 H&amp;E</td>
<td>0</td>
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<tr>
<td>Devaja</td>
<td>2011</td>
<td>60</td>
<td>1H&amp;E + pankreatin at 400µm intervals; maximum 7 pairs</td>
<td>0</td>
</tr>
<tr>
<td>Levenback</td>
<td>2012</td>
<td>418</td>
<td>Pankreatin 40µm interval from H&amp;E</td>
<td>11/418</td>
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</tbody>
</table>

*when initial H&E slide negative
Lymph nodes sectioned perpendicular to long axis at 2.0 mm intervals
Entire lymph node submitted for routine processing
SLN for Routine Processing

- SLN positive
  - No further work up

- SLN negative
  - 5 H&E slides + 2 unstained at 250 μm intervals
    - Levels positive
      - No further work up
    - Levels negative
      - Keratin IHC
Scientific Rationale

  – Modeled the probability of micrometastasis detection for specific sizes in several microsectioning planes
  – Model of H&E and immunohistochemistry at 250μm intervals detected 0.25 mm metastasis with a theoretical probability of 1 and 0.1 mm metastasis with a theoretical probability of 0.46

  – 10 SLN with < 2.0 mm foci metastatic squamous cell ca
  – Model based on median size, 0.9 mm found >95% probability of detection using 5 intervals at 250μm
Role of Immunohistochemistry

  - 23% improved detection
  - Additional H&E levels not studied

- Moore, et al 2003
  - Cytokeratin did not detect additional metastases

- Other studies using H&E and IHC do not specify how micrometastases were detected
Significance of Low Volume Disease

• Experience limited:
  – Terada, et al: (-) SLN subjected to 400μm intervals after groin recurrence detected micrometastasis
  – Tamussino, et al: <1.0 mm metastasis detected by ultrastaging, no completion lymph node dissection; pt recurred
  – Davaja, et al: 3 pts with a single positive SLN (2 pts <2.0 mm metastases; 1 with isolated tumor cells) and no other risk factorsrecurred after opting out of groin dissection
Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study


<table>
<thead>
<tr>
<th>Size</th>
<th>#SLN(+) groins</th>
<th>#SLN(+) groins with completion LND</th>
<th>#non-SLN(+) groins</th>
<th>Non-SLN metastases (%per groin)</th>
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<tr>
<td>Isolated tumor cells</td>
<td>51</td>
<td>24</td>
<td>1</td>
<td>4.2</td>
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<tr>
<td>≤ 1mm</td>
<td>13</td>
<td>10</td>
<td>1</td>
<td>10</td>
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<tr>
<td>&gt;1-2mm</td>
<td>12</td>
<td>9</td>
<td>1</td>
<td>11.1</td>
</tr>
<tr>
<td>&gt;2-5mm</td>
<td>15</td>
<td>15</td>
<td>2</td>
<td>13.3</td>
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<tr>
<td>&gt;5-10mm</td>
<td>16</td>
<td>13</td>
<td>5</td>
<td>38.5</td>
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<tr>
<td>&gt;10mm</td>
<td>9</td>
<td>8</td>
<td>5</td>
<td>62.5</td>
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<tr>
<td>Total</td>
<td>116</td>
<td>79</td>
<td>15</td>
<td>19</td>
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</table>
Summary

• Sentinel lymph node mapping is standard of care for well-selected vulvar carcinoma cases
• Metastasis detection improved by ultrastaging
• Optimal protocol yet to be established
• Significance of low volume disease in the setting of vulvar squamous cell carcinoma still to be determined