ARRO CASE
Operable Vulvar Cancer

Jessica Schuster and Emma Fields
Virginia Commonwealth University
Richmond, VA
Case Presentation: History

• 62 yo female with HIV on HAART
• “Several week history of a growth in my groin”
• Denies change in size, pruritis, or bleeding from site
• PMH: HIV+ - on HAART, Hep C cirrhosis - no meds, HTN, Depression/Anxiety
• PSH: TAH
• Past Gyn History:
  – G1P1, SVD x 1, post-menopausal
  – Prior abnormal paps: many LGSIL paps with HPV+
  – Not currently sexually active
• SH: + smokes 1ppd x 49yrs, drinks beer on weekends, no current illegal drug use, past use of IV heroin 20-30 yrs ago

April 17, 2015
Physical Exam

- **General**: Alert and oriented, No acute distress.
- **Respiratory**: Lungs are clear to auscultation, Respiration is non-labored.
- **Cardiovascular**: Regular rate, Normal rhythm.
- **Gastrointestinal**: Soft, Non-tender.
- **Genitourinary**: Vagina: White, adherent lesion 2x 3cm at vaginal cuff & Mucosa is within normal limits
- **Lymphatics**: Inguinal: No lymphadenopathy.
- **Integumentary**: Warm, Dry.
- **Neurologic**: Alert, Oriented.
- **Psychiatric**: Cooperative, Appropriate Mood & affect
Case Presentation

Pathology

- Colposcopy with biopsies
- **Vaginal cuff, condylomatous lesion 10:00**: High-grade squamous intraepithelial lesion (VAIN II)
- **Vaginal cuff, epithelial scrapings 11:00**: Pronounced HPV cytopathic effect, low-grade squamous intraepithelial lesion (VAIN I)
- **Left vulva, necrotic lesion (specimen #3); punch biopsy**: Squamous cell carcinoma, moderately to well-differentiated

Laboratory Studies

- HIV viral load undetectable
- CD4 count 1200
- CBC and CMP within normal limits
  - Hgb 13.3
Vulvar Cancer

- < 5% of all GYN cancer
  - 4,850 cases/year and 1,030 deaths/year
- Median age 70
- Most common presenting symptoms are pruritis, bleeding, pain or discharge
- 85% squamous cell carcinoma
Vulvar Carcinogenesis

**Keratinizing squamous**
- 80% of cases
- Usually in older women with vulvar dystrophy, lichen sclerosis
- May have p53 mutation
- p16 rarely positive

**Basaloid squamous**
- 20% of cases
- Younger women
- Often times multifocal
- Associated more commonly with HPV infection
- p53 usually negative
- p16 more commonly positive
Vulvar Anatomy

Primary

- Midline: within 1 cm of introitus
  - Mons Pubis
  - Prepuce (2.5%)
  - Clitoris (15%)
  - Vaginal vestibule
  - Posterior forchette /Perineal body (5%)

- Potentially “well-lateralized”
  - Labia Majora/Minora (70%)
  - Bartholin’s glands (2.5%)

Lymph Nodes

- Pattern of spread: Superficial inguinofemoral -> Deep inguinofemoral -> External iliac
  - “Gateway to the pelvis” – Cloquet’s node, most superior deep femoral lymph node
  - Lateralized lesions, rare to have contralateral groin involvement without positive ipsilateral groin

- Clitoris can spread directly to obturators and external illiacs
Vulvar Cancer Risk Factors

- 16, 18, 33 HPV
- Vulvar Intraepithelial Neoplasia (VIN)
- Paget’s disease
- Chronic irritant vaginitis
- Immunosuppression

- Bowen’s disease
- Leukoplakia
- Smoking
- Work in laundry & cleaning industry
- Erythroplasia
- Lichen Sclerosis
Work-up

- History and Physical
- Exam Under Anesthesia
- Biopsy of Primary
- FNA or excisional Biopsy of concerning inguinal nodes
- Pap Smear
- Cystoscopy, Sigmoidoscopy as indicated by clinical symptoms
- Consider Pelvic CT or MRI or PET/CT
  - **Not used in FIGO staging
- CXR
Basic Treatment Overview Resectable Vulvar Cancer

1. **Surgery +/- Adjuvant Therapy**
   - Primary: *Wide Local Excision*
   - Surgery has evolved to become less extensive and less morbid
   - Nodes: Ipsilateral (or bilateral) **inguinal dissection** (or at least sentinel lymph node under the care of an experience Gyn Onc)
     - If depth of invasion < 1mm, may omit inguinal dissection as lymph node risk low
Case Presentation

• Surgical Resection
  – Exam under anesthesia, vaginal biopsy, laser CO2 ablation of the vagina and radical vulvectomy
  – Pathology
    • Invasive Squamous Cell Carcinoma, 2.2 cm in greatest dimension
    • Multifocal, moderately differentiated, keratinizing type
    • Associated VIN III, warty type
    • Depth of stromal invasion by carcinoma: 0.7 cm
    • No lymphovascular or perineural invasion
    • Margins are negative for invasive carcinoma: at least 0.8 cm
      – 12 o'clock to 6 o'clock vulvar skin margins are + VIN III

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Important Pathologic Definitions

- **A: Depth of invasion**
  - Epithelial-stromal junction of adjacent most superficial dermal papillae to deepest point of invasion
  - **Correlates with lymph node metastasis risk**

- **B: Tumor thickness**
  - Granular layer to deepest point of invasion
Risk of Inguinal Nodal Involvement

- **Depth of Invasion (DOI)**
  - <1% for <1mm
  - 6.6% for 1-2mm
  - 8.2% for 2-3mm
  - 22% for 3-4mm
  - At least 25% for > 4 mm

- **Tumor Size**
  - 37.5% > 5 mm
  - 45.8% > 2 cm
  - 54.2% any extension beyond vulva

Clinical exam not sufficient to determine extent of inguinal disease as 11-43% of clinically node negative patients are pathologically node positive.
Case Presentation

• Patient’s vulvar lesion had a **depth of invasion > 1mm**

• **RECOMMENDATION**
  – Left inguinofemoral lymph node dissection followed by right inguinofemoral lymph node dissection if positive node identified

• **PATHOLOGIC FINDINGS**
  – **Left deep femoral lymph node:** Metastatic squamous cell carcinoma, involving two lymph nodes
    • Size of metastasis is 0.9 cm and no extracapsular extension present
  – No right lymph nodes positive
  – Total of 7 lymph nodes resected
Staging ¹

- **AJCC, 7th edition: T Stage**
  - **Tis:** in-situ dz
  - **T1a:** \( \leq 2\text{cm} \), confined to vulva or perineum
    - Stromal invasion \( \leq 1\text{mm} \)
  - **T1b:** >2cm, confined to vulva or perineum
    - Stromal invasion >1mm
  - **T2:** Extension to adjacent perineal structures
    - Ex. Distal 1/3 urethra, distal 1/3 vagina, Anal involvement
  - **T3:** FURTHER extension
    - Ex. Proximal 2/3 urethra, proximal 2/3 vagina, Bladder mucosa, Rectal mucosa, Pelvic bone fixation

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¹ FIGO: N/A

- IA
- IB
- II
- IVA
Staging

- **N Stage**
  - N1a: 1-2 LN met, ≤ 5mm
  - N1b: 1 LN met, >5mm
  - N2a: ≥ 3 LN mets, <5mm
  - N2b: ≥ 2 LN mets, ≥ 5mm
  - N2c: +ECE
  - N3: Fixed or ulcerated LN mets

- **M Stage**
  - M1: Distant mets

FIGO Staging

- III A
- III B
- III C
- IVA
- IV B
Case Presentation

**Imaging**

- Post-operative PET scan
  - No definite evidence of distant metastatic disease
  - Increased metabolic uptake at primary site likely post-surgical change.
Case Summary

- 62-year-old female with well-controlled HIV has FIGO stage IIIB, pathologic T1b N2b M0 Sqcc of the vulva s/p radical vulvectomy and bilateral inguinofemoral dissections that is well-healed and without evidence of residual disease on post-operative exam.
  - Increased risk for locoregional recurrence due to depth of invasion and evidence of deep positive lymph nodes

- Adjuvant Treatment Plan Recommendation: Radiation Therapy
  - Delivered to the primary, bilateral groins and pelvis
  - 45 Gy in 1.8 Gy fractions
  - IMRT to minimize risk of side effects
  - Encouraged smoking cessation and Active Infectious Disease follow-up for HIV management
  - CT simulation scheduled 2 weeks post-operatively
  - Continue joint care with Gyn Onc

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Overview of Adjuvant Therapy Indications

Local ³

- Close or positive margins
- LVI
- Depth of invasion >5mm
- Consider if
  - Planning to treat regional nodes**Add reference to Dusenbery
  - Infiltrating histology
  - Tumor thickness > 1cm
  - High mitotic index
  - Increased keratin

Regional (Inguinal and Pelvis) ⁵

- cN+
- ≥2 pN+
- ECE
  - **Consider concurrent chemotherapy for ≥3 pN+ and ECE
Local Recurrence

- Risk factors found to be significant for local recurrence (LR) s/p radical vulvectomy in *Heaps* et al. surgical series 1990

- **Surgical margin < 8mm**
  - Most powerful predictor of local recurrence
  - ~50% risk of recurrence
  - 91 patients > 8mm margin and none had LR

- **LVSI**
  - ~40% w/LVSI developed LR

- **Depth of invasion > 5mm**

- **Tumor thickness: < 10mm**

- **Infiltrating growth** pattern increase risk vs. pushing border growth pattern

- **Increasing keratin** and > 10 mitoses per high power field
Post-Operative Radiation

- Adjuvant radiation improves local control
  - Retrospective review, Faul et al.
  - 62 patients with close (<8mm) or +margins were treated with XRT or observed
    - Referral for XRT at surgeon discretion
  - XRT: AP/PA, 4867 cGy for close margins and 5854 cGy for positive margins
    - Target: vulva, bilateral inguinals, and low pelvis
  - 58% local recurrence without XRT vs. 16% with XRT

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Regional Radiation

• GOG 37, Homesley et al.
  – 1977-1984, 114 patients
  – Eligibility: Primary invasive squamous cell carcinoma of vulva found to have **positive inguinal lymph nodes**
  – **ALL** completed radical vulvectomy and bilateral inguinal lymph node dissection
  – Randomized: pelvic lymph node dissection vs. adjuvant radiation
    • Pelvic Dissection: Common, External and Internal Iliacs, and Obturator
    • XRT: 4500-5000 cGy to midplane and 2-3 cm depth at inguinal and femoral lymph nodes
      – XRT Target: Common, External, and Internal Iliacs, Obturator, Femoral and Inguinal Nodes, **NO XRT to VULVA**
Regional Radiation

• Overall Survival by Groin Nodal Stage

<table>
<thead>
<tr>
<th>Definition</th>
<th>2-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0 / N1, Negative or normal LN</td>
<td>78%</td>
</tr>
<tr>
<td>cN2, Suspicious LN</td>
<td>52%</td>
</tr>
<tr>
<td>cN3, Fixed, ulcerated LN</td>
<td>33%</td>
</tr>
</tbody>
</table>

• Positive inguinal nodes had 30% risk of pathologically positive pelvic nodes
## Regional Radiation 5-6

<table>
<thead>
<tr>
<th>GOG 37, 1986 2 year outcomes</th>
<th>No XRT</th>
<th>XRT</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groin Recurrence</strong></td>
<td>23.6%</td>
<td>5.1%</td>
<td>This benefit thought to be main contributor to OS improvement</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td>54%</td>
<td>68%</td>
<td>P=0.03, but subset analysis showed that benefit was limited to patient with &gt; 1 LN positive and cLN+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GOG 37, 2009 6 year outcomes</th>
<th>No XRT</th>
<th>XRT</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groin Recurrence</strong></td>
<td>48%</td>
<td>14%</td>
<td>Remained statistically significant</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td>41%</td>
<td>51%</td>
<td>No longer significant, but remained significant for &gt; LN positive, ECE, and cLN+</td>
</tr>
<tr>
<td><strong>Cancer Related Death</strong></td>
<td>51%</td>
<td>29%</td>
<td>Many of late radiation deaths were not related to vulvar cancer</td>
</tr>
</tbody>
</table>
Local Recurrence after Regional XRT

- **GOG 37** \(^5-6\)
  - Coverage of vulva not required
  - 23% of recurrences were local in vulva

- **Dusenbery et al.** \(^7\)
  - Reported vulvar recurrence rate of 48% in patients treated with midline block while receiving adjuvant nodal radiation

- **Recommend vulva local radiation, if treating regional lymph nodes**
Case Presentation

CT SIMULATION

- Supine in frog leg position
- Arms up on a wing board and in an immobilization device
- Wire on all scars
- Anal bb placed
- No bolus placed as IMRT utilized, but in vivo dosimetry with thermoluminescent dosimeters on day 1 (optional)
- Consider IV contrast
- Full bladder for CT simulation and daily treatment
- Consider ITV full and empty bladder
  - in order to compensate for variable bladder fill
Treatment Target

- Classic field borders
  - Wide AP and Narrow PA
    - Superior: Mid – Sacroiliac Joint
    - Inferior: Flash Vulva
  - AP: 2 cm lateral to pelvic brim and encompassing bilateral inguinal/femoral LN stations (~greater trochanter)
    - Supplement dose to inguinal region with two electron fields
  - PA: 2 cm lateral to pelvic brim
    - Blocking femoral heads
Treatment Planning\textsuperscript{8-9}

- **IMRT**\textsuperscript{8-9}
  - GTV (only for pre-op) defined by PET, clinical exam, wire markers
  - CTV primary includes entire vulva and surgical incisions
    - 7mm -2cm around bilateral external iliac, internal iliac, and inguinofemoral nodes
    - 1 cm around entire vulvar region including post-operative bed
      - Pre-sacral nodes included if vaginal involvement to S1-2
      - Peri-rectal nodes included if anal/rectal involvement
  - PTV=CTV + 7-10mm
**Case Presentation**

**Treatment Plan Summary:**
- Adjuvant XRT utilizing IMRT with 2 arcs to 45 Gy in 25 fractions of 1.8 Gy with in-vivo dosimetry verification
- Target: Vulva, bilateral inguinal, external and internal Iliac lymph nodes to level of bifurcation of internal/external iliac
Case Presentation
Case Presentation
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Case Presentation
## Case Presentation – Dose Constraints

<table>
<thead>
<tr>
<th></th>
<th>Dose (Gy)</th>
<th>Goal %</th>
<th>Volume (cm³)</th>
<th>Total Volume</th>
<th>%Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTVFinal</td>
<td>45</td>
<td>95</td>
<td>937.74</td>
<td>973.39</td>
<td>96.3%</td>
</tr>
<tr>
<td>Rt_Fem_Head</td>
<td>50</td>
<td>&lt;5%</td>
<td>0.00</td>
<td>123.32</td>
<td>0.0%</td>
</tr>
<tr>
<td>Lt_Fem_Head</td>
<td>50</td>
<td>&lt;5%</td>
<td>0.00</td>
<td>117.11</td>
<td>0.0%</td>
</tr>
<tr>
<td>Rectum</td>
<td>40</td>
<td>80</td>
<td>51.33</td>
<td>69.43</td>
<td>73.9%</td>
</tr>
<tr>
<td>Bladder</td>
<td>45</td>
<td>&lt;35%</td>
<td>2.21</td>
<td>52.85</td>
<td>4.2%</td>
</tr>
<tr>
<td>SmallBowel</td>
<td>40</td>
<td>30</td>
<td>362.51</td>
<td>1533.9</td>
<td>23.6%</td>
</tr>
<tr>
<td>SmallBowel</td>
<td>45</td>
<td>&lt;195cc</td>
<td>154.74cc</td>
<td>&lt;195cc</td>
<td></td>
</tr>
<tr>
<td>SmallBowel</td>
<td>56</td>
<td>&lt;.03cc</td>
<td>0.00</td>
<td>1533.9</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
# Vulvar Dose

<table>
<thead>
<tr>
<th>Postop Vulva Doses in cGy at 180 cGy/fraction</th>
<th>Vulva</th>
<th>Groin nodes</th>
<th>Pelvic nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Fields</strong></td>
<td>5040</td>
<td>5040</td>
<td>5040**</td>
</tr>
<tr>
<td><strong>Boosts, if needed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neg margin</td>
<td>Pos margin</td>
<td>No ECE*</td>
<td>Early ECE*</td>
</tr>
<tr>
<td>5040 (no boost)</td>
<td>Focal: 5940 &gt; Focal: 6480</td>
<td>5040 (no boost)</td>
<td>5940</td>
</tr>
</tbody>
</table>

*ECE = Extracapsular extension of tumor  
** Dose to pelvic nodes reduced to 4500 if patient is extremely frail
Case Presentation - On Treatment Management

Day of Treatment
• Place TLDs at site of primary tumor & incision
  – **Under bolus
• Check positioning of legs
  – May need extra tattoos or set-up marks on legs to get correct angle
• Check bolus placement

Weekly Visits
• Examine Skin
• Recommend sitz baths
• Silvadene
• Vagisil
• Imodium
• May need temporary catheter
  – **when treating definitive doses
• Vaginal dilator for late stenosis
Case Counseling

• Potential side effects of treatment
  – Radiation dermatitis
    • Increased with increasing BMI
  – Fatigue
  – Cystitis
  – Proctopathy and Diarrhea
  – Vaginal Stenosis
  – Lymphedema
    • ~16% per GOG 37
Resectable Well Lateralized Vulvar Cancer: Wide Local Excision

- < 1mm DOI: Observation
- > 1mm DOI: Ispilateral Inguinal LN Evaluation

Local

- If margins < 8mm, LVS1, or DOI > 5mm: vulvar RT

Regional

- pN0: DONE
- pN+: Complete dissection, bilateral inguinal

ONLY 1 pN+: Observation vs. XRT

> 1 pN+ of cN+: Bilateral inguinal, pelvic, and vulvar XRT

> 2 pN+ or ECE: consider concurrent chemo-XRT

* May consider adjuvant RT
Resectable Midline Vulvar Cancer: Wide Local Excision

- < 1mm DOI: Observation
- > 1mm DOI: Bilateral Inguinal LN Dissection
- If margins < 8mm, LVSI, or DOI > 5mm: vulvar RT

Regional

- pN0: Observation
- ONLY 1 pN+: Observation vs. XRT
- > 1 pN+: Bilateral inguinal, pelvic, and vulvar XRT
- > 2 pN+ or ECE: consider concurrent chemo-XRT
References


