Vulvar Cancer

Clinical Case Conference
Outline

• I. Case Presentation

• II. Anatomy, Epidemiology, Pathology
• III. Clinical Presentation and Work-up
• III. Staging and Prognosis
• IV. Literature Review

• V. Case recommendations and Treatment Planning
The Case

- **HPI:**
  - 3/2011 50 yo p/w painful mass in her right vulva.
  - 6/2011 seen by Gyn Onc, right vulvar mass noted and left and right inguinal lymphadenopathy.
  - 6/2011 CXR negative.
  - 6/2011 CT abdomen pelvis shows irregular soft tissue mass in the right vulva, enlarged right & left inguinal lymph nodes.

- She underwent a right hemivulvectomy and bilateral inguino-femoral LND. Pathology shows:
  - **Lesion 6.5 cm wide, 1.0 cm deep**
  - Moderate to poorly differentiated keratinizing SCC **with LVI**
  - **Margin was 1mm** at the vagina
  - **2/5 LNs positive** on the right but 0/10 on the left
  - pT1bN2b → FIGO IIIb

- Gyn Onc recommends adjuvant chemo-RT
The Case

- **PMH:** Asthma, s/p right oophorectomy for ovarian cyst
- **Meds:** Nicoderm
- **SH:** She has worked in a machine shop. She has a h/o 1-2 PPD tobacco x 25yrs. Occasional alcohol. Prior MJ and meth.
- **FH:** Notable for skin cancer
- **GYN Hx:** Menarche at 15 yo, G2P0. History of birth control pill use for 10 yrs. LMP 2 years ago. Denies history of HRT.
- **PE:**
  - General: Middle-aged woman of normal body habitus.
  - Gyn: s/p right vulvectomy with well-healing surgical scars. There are two pink areas at the edge of the incision at the 12 o’clock position that are 1-2mm in diameter.
Figure 23.1 Pattern of lymphatic spread showing parts of vulva anatomy (curved arrows show lymphatic drainage of different components of vulva, which generally occurs in stepwise fashion from inguinal to pelvic nodes).
Epidemiology

• Per ACS 2013 stats:
  • estimated 4700 new cases
  • ~1000 deaths due to disease
  • 4th most common gyn cancer in women
• <5% of gyn cancer
• Usually 50-70yo women
• Risk factors:
  • HPV – identified in 40% of invasive vulvar cancer
  • Smoking history
  • vulvar dystrophy (incl lichen sclerosus and squamous hyperplasia)
Pathology

• 85% keratinizing squamous cell carcinoma

• 10% melanoma

• Other:
  • Basal cell (WLE only)
  • Adenocarcinoma (often Bartholin’s gland)
  • Merkel cell (aggressive)
  • Sarcoma
Clinical Presentation

- Often presents with:
  - Pruritus
  - Bleeding/discharge
  - Pain
  - Difficult urination/defacation (if locally advanced)

- Initial work-up:
  - Speculum exam
  - 5% acetic acid (+/- toluidine blue)
  - Shave biopsy vs. punch biopsy
    - Shave not sufficient for suspected melanoma
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<tr>
<td>Zoon’s plasma cell vulvitis</td>
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Work-up

• Stepwise progression via lymphatics, *hematogenous spread is uncommon, so distant mets are usually late*
  • No clear indications for CXR

• EUA, cystoscopy, and sigmoidoscopy as needed

• Groin exam is neither sensitive nor specific
  • Spec: Clinically(+) LNs are path(+) in 65-75% (GOG 37 found 76%)
  • Sens: Clinically(-) LNs are path(+) in 10-40% (GOG 37 found 24%)
Lymph node staging

- **IMAGING** to eval lymph nodes:
  - CT pelvis (Land R, *Int J Gynecol Cancer* 2006)
    - sensitivity 58%
    - specificity 75%
  - MRI (Bipat S, *Gynecol Oncol* 2006; Kataoka MY, *Gynecol Oncol* 2010)
    - sensitivity 52-80%
    - specificity 85-89%
  - FDG-PET (Cohn DE, *Gynecol Oncol* 2002)
    - sensitivity 67%
    - specificity 95% **
  - US-guided FNA for suspicious nodes (exam or imaging) but negative does not rule out disease.

- **BOTTOM LINE:** Sensitivity of all imaging modalities available are insufficient to omit surgical evaluation in women with high risk of nodal involvement.
Staging: AJCC 7th ed (2009)

Primary Tumor:
- Tis = in situ
- T1a (FIGO IA): small and superficial
  - ≤ 2 cm in size and
  - ≤ 1mm depth (of stromal invasion)
- T1b (FIGO IB): big OR deep
  - > 2 cm in size, OR
  - any size with >1mm depth
- T2 (FIGO II) - extension to adjacent perineal structures
  - lower/distal 1/3 urethra, or
  - lower/distal 1/3 vagina, or
  - anal involvement
- T3 (FIGO IVA) - extension to:
  - upper/proximal 2/3 of urethra,
  - upper/proximal 2/3 of vagina,
  - bladder mucosa,
  - rectal mucosa, or
  - fixed to pelvic bone

Regional Lymph Nodes (femoral and inguinal)
- N0 = none
- N1 (FIGO IIIA)
  - N1a: 1-2 LN mets, each < 5 mm
  - N1b: 1 LN met ≥ 5 mm
- N2a (FIGO IIIB): 3 or more LN, each < 5 mm
- N2b (FIGO IIIB): 2 or more LN ≥ 5 mm
- N2c (FIGO IIIC): LN with ECE
- N3 (FIGO IVA) - fixed or ulcerated LN

Distant Metastases:
- M0 - none
- M1 (FIGO IVB) - yes (incl pelvic LN met)

Stage Grouping:
- IA - T1a N0 (FIGO IA)
- IB - T1b N0 (FIGO IB)
- II - T2 N0 (FIGO II)
- IIIA - T1-2 N1 (FIGO IIIA)
- IIIB - T1-2 N2a-b (FIGO IIIB)
- IIIC - T1-2 N2c (FIGO IIIC)
- IVA - T3 or N3 (FIGO IVA)
- IVB - M1 (FIGO IVB)
Prognosis


• 1980-1994
• Prospectively followed 504 pts in multiple Italian centers
• Squamous cell vulvar only

• 5-year OS:
  • Stage I – 90%
    Stage II – 75%
    Stage III – 65%
    Stage IV – 30%
• Stage >II, +LNs, LVI → risk factors for any recurrence
Studies to review...

- GOG 37 → RCT for pelvic LND vs. RT for path +inguinal LNs
- GOG 88 → RCT for inguinal LND vs. RT alone
- GOG 173 → prospective phase III inguinal SLN biopsy
- Heaps Gynecol Oncol 1990 → risk factors for recurrence
- Faul IJROBP 1997 → retrospective RT for close/+ margin
- GOG 101 and GOG 205 → neoadjuvant chemoRT for advanced
- GOG 0279 → ONGOING...
GOG 37

• BACKGROUND: Standard = radical vulvectomy and bilateral groin LND → pelvic LND if groin nodes positive BUT high morbidity with extra surgery

• Prospective RCT 1977-?
• 114 pts with squamous vulvar CA undergoing radical vulvectomy and inguinal LN D with + inguinal LNs
• Randomized to:
  • Pelvic LN dissection vs.
  • RT to bilateral groins, mid-plane pelvis, no vulva (45-50Gy, AP/PA)

• Outcomes: survival AND morbidity

GOG 37: RT → survival benefit!

• 2yr Survival: **68% for RT vs. 54% for more surgery** (p=0.03)

![Graph showing survival rates over time.](image)

**Figure 1.** Survival related to type of treatment.

• Most dramatic benefit for those with poor prognostic factors (2+ nodes: 63% vs. 37%; median survival 40 mon vs. 12 mon)

GOG 37: Conclusions

- Groin recurrence: 24% pelvic LND vs. 5% RT
  - Other sites of recurrence NS
  - Vulvar recurrence 9% each group
- In pelvic LND group, rate of +pelvic LNs $\rightarrow$ 28%
- Morbidity similar (though skin maybe under-reported):
  - lymphedema 19% RT vs. 11% surgery (NS)

- Clinical node staging is poor (<50% sensitive)
- RT > pelvic LND for (+) inguinal LNs after inguinal LND
- Consider vulvar RT to decrease vulvar recurrence?

GOG 88

- BACKGROUND:
  - Radical vulvectomy and inguinal LND is standard
  - **BUT** morbidity high (lymphedema, wound)
  - Only 24% of pts with cN0 groin nodes have groin metastases (mostly micro)

- 1986-1990
- 58 pts with squamous vulvar, non-suspicious inguinal LNs
- Randomized to radical vulvectomy followed by:
  - inguino-femoral LND vs.
    - Path+LNs → RT ipsi groin, hemipelvis (per GOG 37)
  - RT to bilateral groin LNs only
    - 50Gy/25 calc to 3cm depth; AP only

*Stehman FB et al, IJROBP 1992.*
GOG 88: Stopped early

- 18% groin failure in RT group (similar to expected 25% pN+).
- All patients who recurred in the groin died of their disease.
- Stopped trial early.

GOG 88: Results

- LRR was 18% with RT vs. 0% with LND (p = 0.03)
- OS was worse with RT vs. LND (p = 0.04)

GOG 88: Conclusions

- Risk factors well balanced though groin RT patients slightly younger ($p = 0.11$) and better KPS ($p = 0.11$)
- 24% of patients in groin node dissection group had + nodes (consistent with GOG 37)
- Inguino-femoral LND > RT to groin in regards to LRR and OS
- Radical vulvectomy AND groin LND with RT for positive nodes will continue to be standard

Reason for RT failure ...

GOG 88: Criticism


- Analyzed pre-treatment CT of 50 gyn patients at UW
- 3 investigators independently estimated depth of 4 femoral vessels (arteries and veins, bilateral) → **6.1cm average depth**
- Used Quatelet Index to estimate node depth based on height/weight
- Applied node depth estimate to GOG 88’s 5 failures
Table 1. Femoral vessel depths in cm*

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<tr>
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<th>LFA</th>
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<td>2.7</td>
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<td>16.5</td>
<td>18.5</td>
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Table 2. Patients with groin failures following prophylactic radiation in a recent GOG study, as adapted from Stehman et al. (18) with permission

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<th>Pt no.</th>
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<th>Ph energy/dose</th>
<th>E energy/dose</th>
<th>Total dose</th>
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<th>E dose</th>
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<td>1</td>
<td>25</td>
<td>6 MeV/2600</td>
<td>12 MeV/2400</td>
<td>5000</td>
<td>5.2</td>
<td>2345†</td>
<td>&lt; 960**</td>
<td>&lt; 3305</td>
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<td>2</td>
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<td>6 MeV/2475</td>
<td>13 MeV/2515</td>
<td>4989</td>
<td>7.3</td>
<td>2014†</td>
<td>&lt; 252**</td>
<td>&lt; 2266</td>
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<td>3</td>
<td>24</td>
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<td>12 MeV/2400</td>
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<td>8.7</td>
<td>1868§</td>
<td>&lt; 240**</td>
<td>&lt; 2108</td>
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GOG 88: Criticism

- 100 women that got pelvic CT
- Prospectively calculated depth of inguinal nodes (to anterior pectineus muscle)

½ of total RT dose given using electrons to spare femoral heads
- 50% isodose line at 5-6cm depth

Figure 1. Representative computed tomography scan showing the measurement of the depth of the inguinal lymph nodes from the skin surface to the pectineus muscle.
GOG 173

• BACKGROUND:
  • Goal to minimize groin node surgery due to 30% risk of lymphedema
  • SLNB established in breast and melanoma

• Prospective, multi-institutional phase III validation trial
• 459 eligible patients
• 1999-2009

• Inclusion Criteria:
  • invasive squamous cell carcinoma of the vulva
  • >1mm depth of invasion
  • 2-6cm primary tumor size
  • inguinal lymph nodes negative on exam

• Primary: estimate negative predictive value of SLNB

Levenbach CF et al, JCO 2012.
GOG 173: Results

- 418/452 (92%) at least one SLN identified
- Incidence of LN mets among women with at least one SLN identified was 31.6% (26% in 2-4cm and 40% in 4-6cm)
- SLN was the only positive node in 73/132 (55.3%) node-positive women.
- Of the 132 node-positive women, 11 had false-negative findings on SLNB (8.3%) → Sensitivity 91.7%
- False negatives less common tumors <4cm
  - (2% for <4cm vs. 7.4% for 4-6cm)

Levenbach CF et al, JCO 2012.
GOG 173: Implications?

- Surgeons say it’s too hard to learn...

BUT...

- 47 GOG institutions
- “no requirement for surgeon skill verification”
- Breast surgeons must have 10-20 cases per yr to be eligible, considered impractical for gyn onc’s treating vulvar cancer
Risk factors for recurrence

Heaps et al, Gynecol Oncol 1990. (UCLA, City of Hope)

• BACKGROUND: Standard = radical vulvectomy with 3cm normal tissue margin **BUT** severe impact on organ function (clitoris, urethra, anus) and body image

• Retrospective review of 135 cases of vulvar cancer Stage I-IV
  • 110 were stage I-II
  • Treated 1957-1985
• Assessed factors associated with recurrence after surgery
Heaps et al, Gynecol Oncol 1990.

- Surgical margin >8mm → major prognostic factor for vulvar recurrence ... 48% (21/44) if <8mm vs. 0% (0/91) if ≥8mm)

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<td>Margin</td>
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<td>Depth of invasion</td>
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<td>Tumor thickness</td>
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<td>Growth pattern</td>
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<td>Vascular invasion</td>
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<td>Grade</td>
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- TABLE 7

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<th>Lymph-vascular invasion</th>
<th>Vulvar recurrence</th>
<th>Total</th>
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<td>Present</td>
<td>7 (39%)</td>
<td>18</td>
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<tr>
<td>Absent</td>
<td>14 (12%)</td>
<td>117</td>
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<tr>
<td>Total</td>
<td>21</td>
<td>135</td>
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* P = 0.0031.
GOG 101

- BACKGROUND:
  - T3/T4 → pelvic exent → operative mortality 10%
  - N2/N3 →

- 1989-1994
- Prospective phase II trial
- 96 pts with vulvar CA with either T3/T4 unresectable or N2/N3
- Split course chemo-RT → resection
  - Cisplatin and 5FU
  - RT (AP/PA) was split course 170cGy/fx to 4380cGy (daily-BID)
- Median F/U of 50 mon among those living

Staging: AJCC 7th ed (2009)

T2***  II  Tumor of any size with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)

T3****  IVA  Tumor of any size with extension to any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone

***FIGO uses the classification T2/T3. This is defined as T2 in TNM.
****FIGO uses the classification T4. This is defined as T3 in TNM.
Followed by surgery to remove tumor and inguino-femoral LND within 4-8wks

Complete response → only biopsy of primary + inguino-femoral LND required (though most pts still got WLE)

No response and still unresectable → 2000cGy more AP/PA

Resected primary with micro + margins → further surgery or 1000-1500cGy RT boost
GOG 101: T3/T4

- 71 patients evaluable in T3/T4 group
- Primary outcomes:
  - Exenterative converted to non-exenterative surgery
  - Morbidity

- cCR in 34/71 (47%), and of these 22/31 (70%) had pCR
- Of the 50 pts felt initially to need exenteration (T4) only 1 subsequently needed exent and 2 needed colostomy.
- Only 2/71 (3%) had residual unresectable disease
- At 50 mon f/u:
  - LRR was 33%
  - DFS was 55%
GOG 205

- Phase II trial of unresectable T3 or T4, any N
- 58 evaluable pts
- Neoadjuvant RT with concurrent weekly cisplatin, then surgery
- RT dose 57.6 Gy (20% escalation from GOG 101)
  - AP/PA to vulva, inguinal-femoral, lower pelvic LNs

Results:
- 40/58 (69%) completed study treatment.
- cCR 37/58 (64%) → pCR 29/37 (78%); overall pCR 29/58 (50%)
- Conclusion: chemoRT leads to high CR and acceptable toxicity
- NOTE: 64% cCR rate is an increase from the ~48% seen in GOG 101. pCR of 50% is an increase from the 31% in GOG 101.
  - Higher dose? No break?

Moore DH, Gynecol Oncol 2012.
GOG 0279

Primary objective: To determine the efficacy of cisplatin, gemcitabine, and IMRT in achieving a pCR when used for the primary treatment of locally-advanced SCC of the vulva.

ONGOING...
Recommendations: Early Stage

• <1mm thick on WLE → no LND may be acceptable.
  • All others should have LND.
• Well-lateralized (>1-2cm from midline) tumors can have unilateral inguino-femoral LND.
  • Central tumors need bilateral LND.
• If groin LNs involved, contralateral groin LND is needed.
• SLN Bx promising to reduce morbidity of dissection
• Consider adjuvant RT to primary for close/pos mgn, LVI, invasion over 5mm
• Consider adjuvant RT for inguino-femoral and pelvic LNs if >1 LN involved, ECE, or bulky.
# AP/PA

<table>
<thead>
<tr>
<th>Field</th>
<th>Borders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wide AP</strong></td>
<td>Superior: mid-sacroiliac joint to include external and internal iliac node involvement; L4–L5 to include the common iliac nodes if internal/external iliac nodes suspicious or positive</td>
</tr>
<tr>
<td></td>
<td>Inferior: flash entire vulva or inferior margin of the tumor (whichever is lower)</td>
</tr>
<tr>
<td></td>
<td>Lateral: 2 cm beyond the widest point of the pelvic inlet on the PA field, and greater trochanter to include inguinal lymph nodes in the AP field</td>
</tr>
<tr>
<td><strong>Narrow PA</strong></td>
<td>Superior: same as AP field</td>
</tr>
<tr>
<td></td>
<td>Inferior: same as AP field</td>
</tr>
<tr>
<td></td>
<td>Lateral: off femur and match supplemental electron fields</td>
</tr>
<tr>
<td><strong>Supple electron</strong></td>
<td>Anterior electron fields to the lateral inguinal region</td>
</tr>
<tr>
<td></td>
<td>Matched with the exit PA field</td>
</tr>
<tr>
<td></td>
<td>Energy based on CT depth of femoral vessels</td>
</tr>
<tr>
<td><strong>Cone down</strong></td>
<td>Primary tumor and involved inguinal lymph nodes plus 2- to 3-cm margin after 45 Gy to the pelvis</td>
</tr>
</tbody>
</table>

- All fields should be irradiated on daily basis
- Bolus material should be used to ensure adequate dose to the superficial portions of the groin or tumor
3D conformal
IMRT

- CTV: 1-cm margin around entire vulvar region and bilateral external iliac, internal iliac, and inguino-femoral nodes
- PTV: CTV plus 1 cm
IMRT

- CTV included lower common iliac, bilateral external iliac, internal iliac, and inguino-femoral nodal areas, along with the entire vulvar region.
- Margin 1 cm around blood vessels
- Margin 2 cm in inguino-femoral nodal region.
- 1-2 cm flash
- Inferiorly, CTV expanded 1-2 cm beyond vulva (for swelling)
  - 1 cm bolus used for treatment
RT Planning/Dose

- Sim full and empty bladder
- Frog leg?

<table>
<thead>
<tr>
<th>Setting</th>
<th>Scenario</th>
<th>Dose of RT (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>-</td>
<td>45–50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Postoperative</td>
<td>Microscopic residual</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Extracapsular external or N&lt;sup&gt;+&lt;/sup&gt;</td>
<td>55–60</td>
</tr>
<tr>
<td></td>
<td>Gross residual</td>
<td>65–70</td>
</tr>
<tr>
<td>Definitive</td>
<td>Concurrent chemoradiation</td>
<td>60–65</td>
</tr>
</tbody>
</table>

- Neoadjuvant dose 45Gy to nodes (or 50Gy pN+), 64Gy to primary CONCURRENTLY with cisplatin/ gemcitabine(?) → assess response → surgery or more (?) chemoRT for residual
Case SS: RT plan

<table>
<thead>
<tr>
<th>Prescription ID</th>
<th>Physician's Intent</th>
<th>Physician's Intent</th>
<th>Physician's Intent</th>
<th>Physician's Intent</th>
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</thead>
<tbody>
<tr>
<td>Predecessor ID</td>
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<tr>
<td>Status</td>
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<td>Pelvis</td>
<td>inguinal region</td>
<td>Vulva</td>
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<td>probable AP/PA</td>
<td>en face electron</td>
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<tr>
<td>Depth</td>
<td>% Isolevel</td>
<td>% Isolevel</td>
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<tr>
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<td>200.00</td>
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<tr>
<td>Prescribed Dose / Fraction [cGy]</td>
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<td>Planned No. Fractions</td>
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<tr>
<td>Fractions per Day</td>
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<tr>
<td>Delivered Dose to Date [cGy]</td>
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<td>Delivered No. Fractions to Date</td>
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<tr>
<td>Remaining Dose [cGy]</td>
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<tr>
<td>Remaining No. Fractions</td>
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<tr>
<td>Planned Total Dose [cGy]</td>
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<tr>
<td>Note</td>
<td>mixed energy</td>
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</table>
Case

• Adjuvant radiotherapy without concurrent chemo given that she is considered a poor candidate.

• Completed RT 6/29/12

• Recurred bilateral groins 11/2012

• Passed away early 2013
Questions?

Thank you!