Symptomatic lower-extremity lymphedema following treatment of gynecologic malignancies

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Pelvic Lymphadenectomy
Introduction

- Lymphedema – chronic, progressive condition characterized by the accumulation of protein rich fluid in superficial tissues
  - Stage I: edema is mild; fluid accumulates throughout the day but resolves overnight
  - Stage II: the lymphedema is always present but varies in severity
  - Stage III: disease is characterized by persistent, moderate-to-severe edema of the involved limb
Lower Extremity Lymphedema
Background

- Incidence uncertain
  - Limited prospective data
  - Retrospective data suffers from under-reporting
  - Lack of uniform system of documenting lymphedema

- Associated with removal of regional nodes/ adjuvant therapy but risk factors uncertain
  - Pre-op: race, age, BMI, medical condition
  - Operative: site/number of nodes, use of drains
  - Post-op: pathologic status of nodes, number removed, use of adjuvant therapy, infection
Background

- Comprehensive retrospective study of 487 women treated for GYN cancer
  - 36% incidence of symptomatic lymphedema
  - Highest rates with vulvar cancer

- Consequences
  - 27% financial burden
  - 79% change in clothing
  - 51% altered daily activities

Ryan M et al ONF. 2003; 30:417-423
GOG 195
- 137 pts with inguinal LND underwent standard closure vs. Tisseel® fibrin sealant
- Ankle, mid calf, and mid thigh circumference obtained pre-op then post-op for 6 months
- Lymphedema characterized as:
  - Mild: greater than baseline but < 3cm
  - Moderate: 3 to 5cm increase
  - Severe: > 5 cm

*Carlson et al. Gynecol Oncol 2008;110:76-82*
Vulvar Cancer

- GOG 195 Results:
  - Grade 2/3 lymphedema
    - 60% Tisseel® arm
    - 67% suture arm
    - 76% by 6 weeks, 91% by 3 months
  - Increased risk with:
    - Race-100% in african-americans
    - Vulvar Infection
    - Age, weight, and use of postoperative radiation were not associated with lymphedema.

*Carlson et al. Gynecol Oncol 2008;110:76-82*
Cervical Cancer

- 21% incidence in 54 patients undergoing radical hysterectomy/PLND
- Over 50% symptomatic
- 8 fold increased risk of lymphedema following rad hyst/PLND
- 25% reported stress due to lymphedema
  - Bergmark et al. Int J Gynecol Cancer 2006;16:1130-9
Endometrial Cancer

- Reports in the literature are rare and retrospective
- Incidence reported between 5-10%
  - Ryan M et al. ONF. 2003; 30:417-423
Endometrial Cancer: MSKCC experience

- Retrospective chart review of all patients with uterine corpus cancer managed over a 12-year period (1/93–12/04).
- All patients had a hysterectomy as part of their therapy.
- Lower extremity lymphedema described by the physician or reported by the patient.
- Excluded lymphedema secondary to medical conditions: cardiovascular and renal disease, venous thrombosis, etc.

*Abu-Rustum et al. Gynecol Oncol; 103:714-8. 2006*
Endometrial Cancer: MSKCC experience

- Lymphedema was noted at a median of 5.3 months after surgery (range, 1–32 months)
- Symptomatic lymphedema was limited to patients who had 10 or more regional lymph nodes removed 16/469 (3.4%)
- Lymphedema was unilateral in 11 patients (69%) and bilateral in 5 (31%)
- Grade 1 in 12 patients (75%) and grade 2 in 4 (25%).
- Age, weight, stage, type of hysterectomy, and type of postoperative adjuvant therapy were not associated with lymphedema.
The LeG Study was a multi-institutional prospective study of women newly diagnosed with endometrial, cervical and vulvar cancer who received surgery with a lymphadenectomy as primary intervention with planned two years of follow up.

This study was funded by NCI GOG and NIH R01 CA162139.
Objectives  GOG 244: LeG Study

- **Primary:** To prospectively evaluate the incidence of, and potential risk factors for lymphedema of the lower extremity

- **Secondary:**
  - To explore the effect that LLE has on quality of life (FACT-G + disease specific subscale)
  - To evaluate the association of LLE with self-reported symptoms as measured with the Gynecologic Cancer Lymphedema Questionnaire (GCLQ)

- June 2012- November 2014
GOG 244: Treatment Plan

- Serial circumferential measurements performed at 10cm intervals from the heel to the inguinal crease 4-6 weeks postop then q 3 mos. x 1 year, and q6 mos. for an additional year.

- Leg volume calculated from the circumferential measurements based on the formula for a truncated cone: \( V = (h)(C^2 + Cc + c^2)/12(\pi) \) (where \( h \) = height of the segment; \( C \) = circumference at top of segment; \( c \) = circumference at bottom of segment)

- Leg volume change (LVC) was the difference in summation of each truncated cone volume over time

- Logistic Regression was used for comparison of other variables, \( p<0.05 \) considered significant
GOG 244: Data collection

- Data collected regarding possible risk factors for the development of lymphedema:
  - Node count
  - Laterality of nodes removed
  - Lymph node status (metastases)
  - Perioperative infection, lymphocyst formation, use of closed suction drainage
  - BMI
  - Post-op radiation/chemotherapy.

- Quality of life (GCLQ) was assessed at baseline, 4 weeks postoperatively, and then every 3 months for the first year and every 6 months for an additional year.
Gynecologic Cancer Lymphedema Questionnaire

The following questions regarding your experiences with movement, use and sleep in the past 4 weeks.
1. Do you have limited movement of your hip?  Yes □ No □
2. Do you have limited movement of your knee?  Yes □ No □
3. Do you have limited movement of your ankle?  Yes □ No □
4. Do you have limited movement of your foot?  Yes □ No □
5. Do you have limited movement of your Toes?  Yes □ No □
6. Does your leg or foot feel weak?  Yes □ No □

The following questions relate to symptoms you might experience on your foot, leg, hip, groin or your lower body in the past 4 weeks. Please check one answer per line.
7. Have you experienced tenderness?  Yes □ No □
8. Have you experienced swelling?  Yes □ No □
9. Have you experienced swelling with pitting?  Yes □ No □
10. Have you experienced redness?  Yes □ No □
11. Have you experienced blistering?  Yes □ No □
12. Have you experienced firmness/tightness?  Yes □ No □
13. Have you experienced increased temperature in your leg?  Yes □ No □
14. Have you experienced heaviness?  Yes □ No □
15. Have you experienced numbness?  Yes □ No □
16. Have you experienced stiffness?  Yes □ No □
17. Have you experienced aching?  Yes □ No □
18. Have you experienced hip swelling?  Yes □ No □
19. Have you experienced groin swelling? (genital, labia/vulvar)  Yes □ No □
20. Have you experienced pockets of fluid developed?  Yes □ No □

The following questions pertain to the actions you have taken or are taking for lymphedema in the past 4 weeks. Please circle one answer per line.
21. Have you been diagnosed to have Lymphedema (on your leg)?  Yes □ No □
    If Yes, please answer question 22 and 23. Otherwise stop here.
22. Are you undergoing or have you taken treatment for Lymphedema?  Yes □ No □
    If Yes, go to question 23. Otherwise stop here.
23. Please mark which following treatment(s) you are taking or have taken for lymphedema:
    a. Directed exercise  Yes □ No □
b. Compression Garment  Yes □ No □
c. Manual Lymphatic Drainage  Yes □ No □
d. Specialized Lymphedema Massage  Yes □ No □
e. Skin Care Instruction  Yes □ No □
f. Multi-Limb Bandaging-MLB (wrapping/lower limb padding)  Yes □ No □

24. Please mark if you have received any of the following information or training for your lymphedema:
    a. Nurse Education  Yes □ No □
b. Physical Therapy Consult or Occupational therapy  Yes □ No □
c. Lymphedema Specialist  Yes □ No □
Methods: Gynecologic Cancer Lymphedema Questionnaire (GCLQ):

- GCLQ Scores for total current symptoms and clustered symptoms were calculated to describe the most prominent symptoms associated with LLE diagnosis and changes over time.

- The clinical cut off score of 4-point change from baseline was used based on the validation study [Carter et al., 2010].

- Association between changes in the GCLQ scores over time with patient-reported LLE and LVC was evaluated with a linear mixed model, adjusted for assessment time and disease site.
## Results: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>Endometrial (n=672)</th>
<th>Cervical (n=124)</th>
<th>Vulvar (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>X = 61 years (28-91)</td>
<td>X = 46 yrs (25-83)</td>
<td>X = 59 yrs (35-88)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Mean (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>X = 61 years (28-91)</td>
<td>X = 46 yrs (25-83)</td>
<td>X = 59 yrs (35-88)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>White</td>
<td>82% (n=551)</td>
<td>73% (n=90)</td>
<td>88% (n=22)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>10% (n=64)</td>
<td>5% (n=6)</td>
<td>4% (n=1)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>3% (n=17)</td>
<td>8% (n=10)</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>Other/Unspecif</td>
<td>6% (n=40)</td>
<td>15% (n=18)</td>
<td>8% (n=2)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>Non-Hispanic</td>
<td>93% (n=628)</td>
<td>82% (n=102)</td>
<td>92% (n=23)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>5% (n=33)</td>
<td>15% (n=19)</td>
<td>8% (n=2)</td>
</tr>
<tr>
<td></td>
<td>Other/Unspecif</td>
<td>2% (n=11)</td>
<td>2% (n=3)</td>
<td>--------------</td>
</tr>
<tr>
<td><strong>Stage of Disease</strong></td>
<td>Stage I</td>
<td>80% (n=540)</td>
<td>98% (n=122)</td>
<td>64% (n=16)</td>
</tr>
<tr>
<td></td>
<td>Stage II</td>
<td>5% (n=36)</td>
<td>2% (n=2)</td>
<td>12% (n=3)</td>
</tr>
<tr>
<td></td>
<td>Stage III</td>
<td>13% (n=89)</td>
<td></td>
<td>20% (n=5)</td>
</tr>
<tr>
<td></td>
<td>Stage IV</td>
<td>1% (n=7)</td>
<td></td>
<td>4% (n=1)</td>
</tr>
</tbody>
</table>
1054 Patients were enrolled

- 167 cervical cancer
  - 9 not eligible
  - 158 had lymphadenectomy
    - 20 didn’t have valid pre or post op measurements
    - 138 evaluable for LVC

- 843 endometrial cancer
  - 43 not eligible
  - 13 did not have surgery
  - 787 had lymphadenectomy
    - 53 didn’t have valid pre or postop measurements
    - 734 evaluable for LVC

- 44 vulvar cancer
  - 2 not eligible
  - 42 had lymphadenectomy
    - 42 evaluable for LVC
## Results GOG 244: LeG Study

### Leg Volume Change: Uncensored

<table>
<thead>
<tr>
<th>LVC</th>
<th>Cervical ( n=138 )</th>
<th>Endometrial ( n=734 )</th>
<th>Vulvar ( n=42 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10%</td>
<td>35% (48)</td>
<td>34% (246)</td>
<td>43% (18)</td>
</tr>
<tr>
<td>&gt; 15%</td>
<td>25% (35)</td>
<td>19% (140)</td>
<td>19% (8)</td>
</tr>
<tr>
<td>&gt; 20%</td>
<td>12% (17)</td>
<td>11% (79)</td>
<td>14% (6)</td>
</tr>
</tbody>
</table>
Definition of LLE

- Initial definition of LLE was proposed as limb volume change (LVC) of ≥10%
  - 30% (n=245/821) had leg volume increase ≥10% from baseline
  - 19% (47/245) had patient-reported LLE on the GCLQ
  - LVC is a surrogate for but not equal to LLE

- Due to concerns about measurement error and potential confounding factors, the following steps were taken to ensure identifying true LLE:
  - Patients with DVTs, surgical infection, or vascular insufficiency were removed,
  - BMI ≥10% increase was censored within this analysis
  - Based on GCLQ’s ability to distinguish between those with and without patient-reported LLE, and its demonstrated predictive value, the GCLQ was included with LVC
## Results GOG 244: LeG Study

Medical Diagnosis associated with increased LVC

<table>
<thead>
<tr>
<th>Medical Diagnosis</th>
<th>Cervical</th>
<th>Endometrial</th>
<th>Vulvar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Insufficiency (VI)</td>
<td>3 (0.4%)</td>
<td>1 (2.38%)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>9 (6.5%)</td>
<td>22 (3%)</td>
<td>11 (26%)</td>
</tr>
<tr>
<td>VTE</td>
<td>1 (0.7%)</td>
<td>4 (0.54%)</td>
<td>2 (4.75%)</td>
</tr>
<tr>
<td>Infection + VI</td>
<td>1 (0.14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection + VTE</td>
<td></td>
<td>2 (0.27%)</td>
<td></td>
</tr>
<tr>
<td>VTE + VI</td>
<td>1 (0.7%)</td>
<td>1 (0.14%)</td>
<td></td>
</tr>
<tr>
<td>BMI &gt;10%</td>
<td>1</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>12</td>
<td>48</td>
<td>15</td>
</tr>
</tbody>
</table>
GOG 244: Censored data

1054 Patients were enrolled

167 cervical cancer
- 9 not eligible
  - 158 had lymphadenectomy
    - 20 didn’t have valid pre or post op measurements
    - 11 had DVT, inf. or VI
    - 1 censored for BMI
  - 126 evaluable for LVC

843 endometrial cancer
- 43 not eligible
  - 13 did not have surgery
  - 787 had lymphadenectomy
    - 53 didn’t have valid pre or postop measurements
    - 33 had DVT, inf. or VI
    - 15 censored for BMI
  - 686 evaluable for LVC

44 vulvar cancer
- 2 not eligible
  - 42 had lymphadenectomy
    - 14 developed DVT, inf. or VI
    - 1 censored for BMI
  - 27 evaluable for LVC
## Results GOG 244: LeG Study

### Limb Volume Change: Censored Medical Dx and BMI

<table>
<thead>
<tr>
<th>LVC</th>
<th>Cervical n=126</th>
<th>Endometrial n=686</th>
<th>Vulvar n=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10%</td>
<td>43 (34.1%)</td>
<td>231 (33.7%)</td>
<td>11 (40.7%)</td>
</tr>
<tr>
<td>&gt; 15%</td>
<td>31 (24.6%)</td>
<td>131 (19.1%)</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>&gt; 20%</td>
<td>13 (10.3%)</td>
<td>75 (10.9%)</td>
<td>3 (11.1%)</td>
</tr>
</tbody>
</table>
Results GOG 244: LeG Study

Data concerns: Lost to follow up

<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Endometrial</th>
<th>Vulvar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>138</td>
<td>734</td>
<td>42</td>
</tr>
<tr>
<td>Postop</td>
<td>124</td>
<td>669</td>
<td>38</td>
</tr>
<tr>
<td>3 months</td>
<td>103</td>
<td>576</td>
<td>30</td>
</tr>
<tr>
<td>6 months</td>
<td>104</td>
<td>543</td>
<td>34</td>
</tr>
<tr>
<td>9 months</td>
<td>91</td>
<td>504</td>
<td>31</td>
</tr>
<tr>
<td>12 months</td>
<td>88</td>
<td>512</td>
<td>29</td>
</tr>
<tr>
<td>18 months</td>
<td>83</td>
<td>448</td>
<td>21</td>
</tr>
<tr>
<td>24 months</td>
<td>66 (48%)</td>
<td>400 (54%)</td>
<td>17 (40%)</td>
</tr>
</tbody>
</table>
## Results: GCLQ Compliance Rates

<table>
<thead>
<tr>
<th>GCLQ Assessment Time Point</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>98%</td>
</tr>
<tr>
<td>6 weeks</td>
<td>93%</td>
</tr>
<tr>
<td>3 months</td>
<td>83%</td>
</tr>
<tr>
<td>6 months</td>
<td>81%</td>
</tr>
<tr>
<td>9 months</td>
<td>74%</td>
</tr>
<tr>
<td>12 months</td>
<td>74%</td>
</tr>
<tr>
<td>18 months</td>
<td>67%</td>
</tr>
<tr>
<td>24 months</td>
<td>62%</td>
</tr>
</tbody>
</table>
Results GOG 244: LeG Study

- Concerns about data elements/conclusions
  - LVC is a surrogate for but ≠ Lymphedema

- Endometrial cancer
  - Largest cohort: used for subset analysis
  - The percentage of patients whose GCLQ total score increased ≥4 was significantly associated with lymphedema diagnosis (p<0.001)
  - Change in score noted prior to diagnosis of LLE
Results GOG 244: LeG Study

- Defined “True lymphedema”
  - PRO of “lymphedema” on GCLQ (12%)
  - GCLQ score increased ≥4 and LVC ≥ 10% (8%)
  - Total lymphedema rate: 20%

Cervical Cancer: 31/124 (25%)
Endometrial Cancer: 127/672 (18%)
Vulvar Cancer: 10/25 (40%)
Definition of LLE

- **New definition of True LLE**
  - Any patient reporting LLE diagnosis
  - LVC increase $\geq 10\%$ combined with GCLQ increase ($\geq 4$ points) from baseline in patients without a formal LLE diagnosis
GOG 244: OTHER FINDINGS
Onset of True Lymphedema

<table>
<thead>
<tr>
<th>Assessment Time</th>
<th>Cervical</th>
<th></th>
<th>Endometrial</th>
<th></th>
<th>Vulvar</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>6 weeks</td>
<td>16</td>
<td>51.6</td>
<td>57</td>
<td>44.9</td>
<td>8</td>
<td>80.0</td>
<td>81</td>
<td>48.2</td>
</tr>
<tr>
<td>3 months</td>
<td>7</td>
<td>22.6</td>
<td>26</td>
<td>20.5</td>
<td>2</td>
<td>20.0</td>
<td>35</td>
<td>20.8</td>
</tr>
<tr>
<td>6 months</td>
<td>5</td>
<td>16.1</td>
<td>20</td>
<td>15.7</td>
<td>.</td>
<td>.</td>
<td>25</td>
<td>14.9</td>
</tr>
<tr>
<td>9 months</td>
<td>3</td>
<td>9.7</td>
<td>12</td>
<td>9.4</td>
<td>.</td>
<td>.</td>
<td>15</td>
<td>8.9</td>
</tr>
<tr>
<td>12 months</td>
<td>.</td>
<td>.</td>
<td>4</td>
<td>3.1</td>
<td>.</td>
<td>.</td>
<td>4</td>
<td>2.4</td>
</tr>
<tr>
<td>18 months</td>
<td>.</td>
<td>.</td>
<td>8</td>
<td>6.3</td>
<td>.</td>
<td>.</td>
<td>8</td>
<td>4.8</td>
</tr>
</tbody>
</table>

95% occurred in the first year of follow up
## Results: Surgical Approach

Endometrial Cancer: No difference in LLE vs approach

<table>
<thead>
<tr>
<th>Surgical Approach</th>
<th>Lymphedema Present</th>
<th>Lymphedema Absent</th>
<th>Total N=672</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotic</td>
<td>348 (63.9%)</td>
<td>74 (58.3%)</td>
<td>422 (62.8%)</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>92 (16.9%)</td>
<td>21 (16.5%)</td>
<td>113 (16.8%)</td>
</tr>
<tr>
<td>Open</td>
<td>105 (19.3%)</td>
<td>32 (25.2%)</td>
<td>137 (20.4%)</td>
</tr>
</tbody>
</table>
## Results: Surgical Approach

Cervical Cancer: No difference in LLE vs approach

<table>
<thead>
<tr>
<th>Surgical Approach</th>
<th>Lymphedema Present</th>
<th>Lymphedema Absent</th>
<th>Total N=672</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotic</td>
<td>45 (50.6%)</td>
<td>14 (45.2%)</td>
<td>59 (49.2%)</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>17 (19.1%)</td>
<td>5 (16.1%)</td>
<td>22 (18.3%)</td>
</tr>
<tr>
<td>Open</td>
<td>27 (30.3%)</td>
<td>12 (38.7%)</td>
<td>39 (32.5%)</td>
</tr>
</tbody>
</table>
Results GOG 244: LeG Study

- Comparing risks for lymphedema in Cervical & Endometrial Cancer (larger numbers/similar surgery)
  - No difference in age, race, performance status, stage, weight, serum albumin, or surgical blood loss
  - No difference in radiation received for cervical or endometrial cancer through 3 months and 9 months, respectively
  - No difference in node count ≤ 8 (n=75) vs >8 (n=597), but note a trend for endometrial (p=0.069)
Discussion  GOG 244: LEG Study

- The incidence of LLE is under recognized
- This study helps distinguish between an increase in limb volume and true lymphedema – GCLQ
- Most extensive attempt to prospectively identify the true incidence of LLE and the associated risks
- Data challenges some common beliefs concerning lymphedema: Node count, Adjuvant radiation
Acknowledgements

- R01 Investigators
  - RR Barakat
  - J Armer
  - J Carter
  - S Lockwood
  - B Stewart
  - L Wenzel
  - S Nolte
  - D Alberts

- GOG Stats Members
  - J Kauderer
  - H Huang
  - A Hutson

- High Accrual Sites
  - J Walker - OUHS
  - A Fleury - WCC
  - A Bonebrake - CoxHealth
  - J Soper - UNC
  - C Mathews - WIH
  - O Zivanovic - MSKCC
  - WE Richards - SJCHS
  - A Tan - MMCCOP