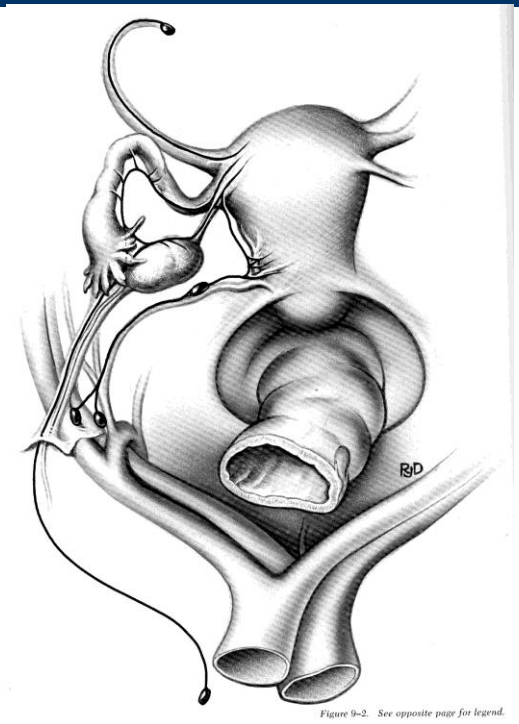
Symptomatic lower-extremity lymphedema following treatment of gynecologic malignancies



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Strategic Alliance Partners

IGCS
INTERNATIONAL GYNECOLOGIC CANCER SOCIETY

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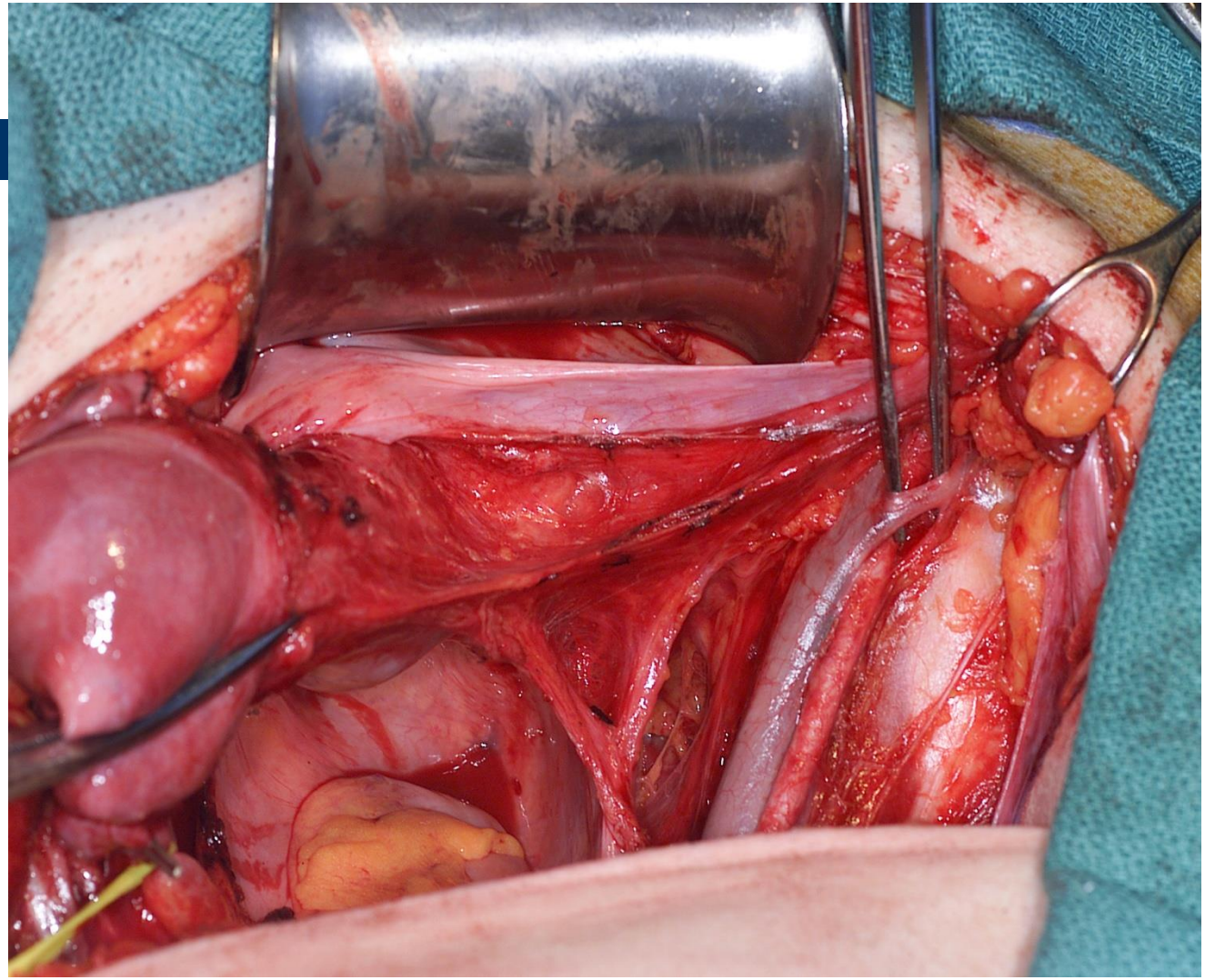
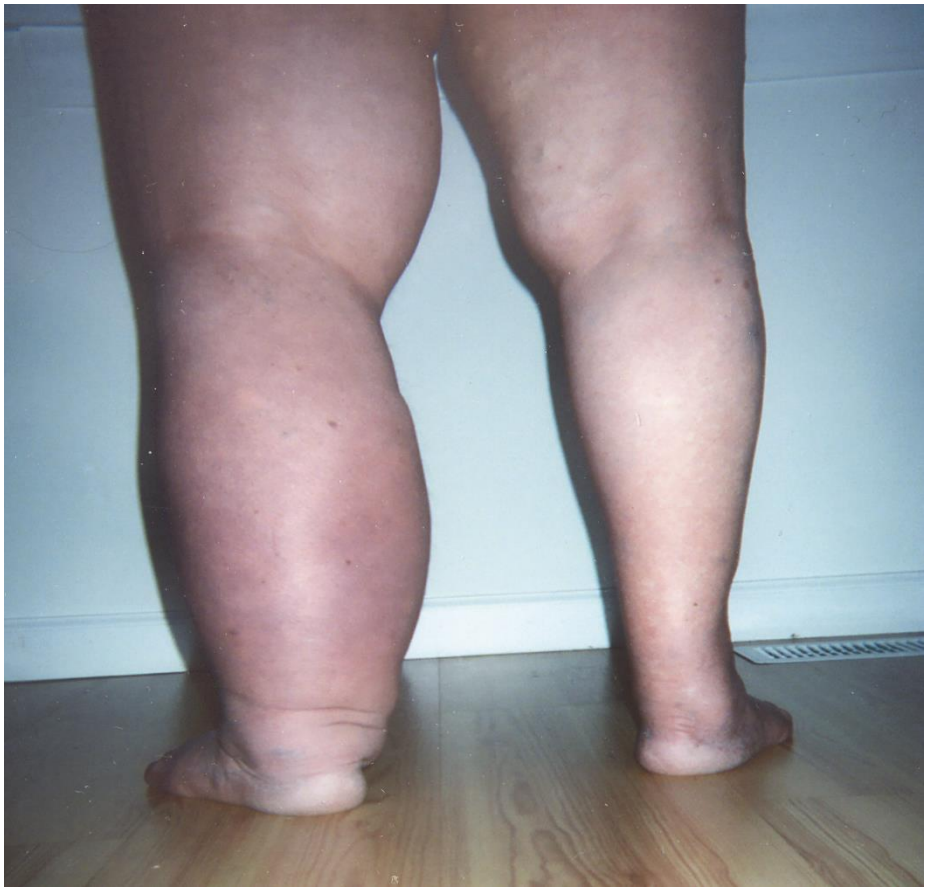
Pelvic Lymphadenectomy



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

Vulvar Cancer

- 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

- Cervical Cancer
  - 21% incidence in 54 patients undergoing radical hysterectomy/PLND
  - Over 50%symptomatic
    - ***Werngren et al. Scand J. Plast. 1994: 28:289-293***
  - 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***
  - ***Fujiwara et al. Cancer. 2003; 13:61-6***

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.

GOG 244 - The Lymphedema and Gynecologic (LeG) Cancer Study

- 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.

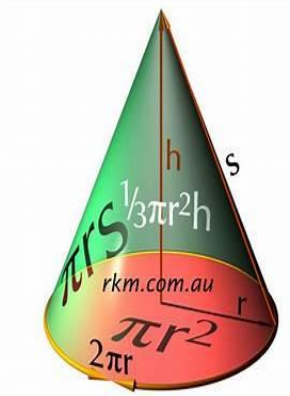
Objectives GOG 244: LeG Study

- 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?

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 you 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 ☐

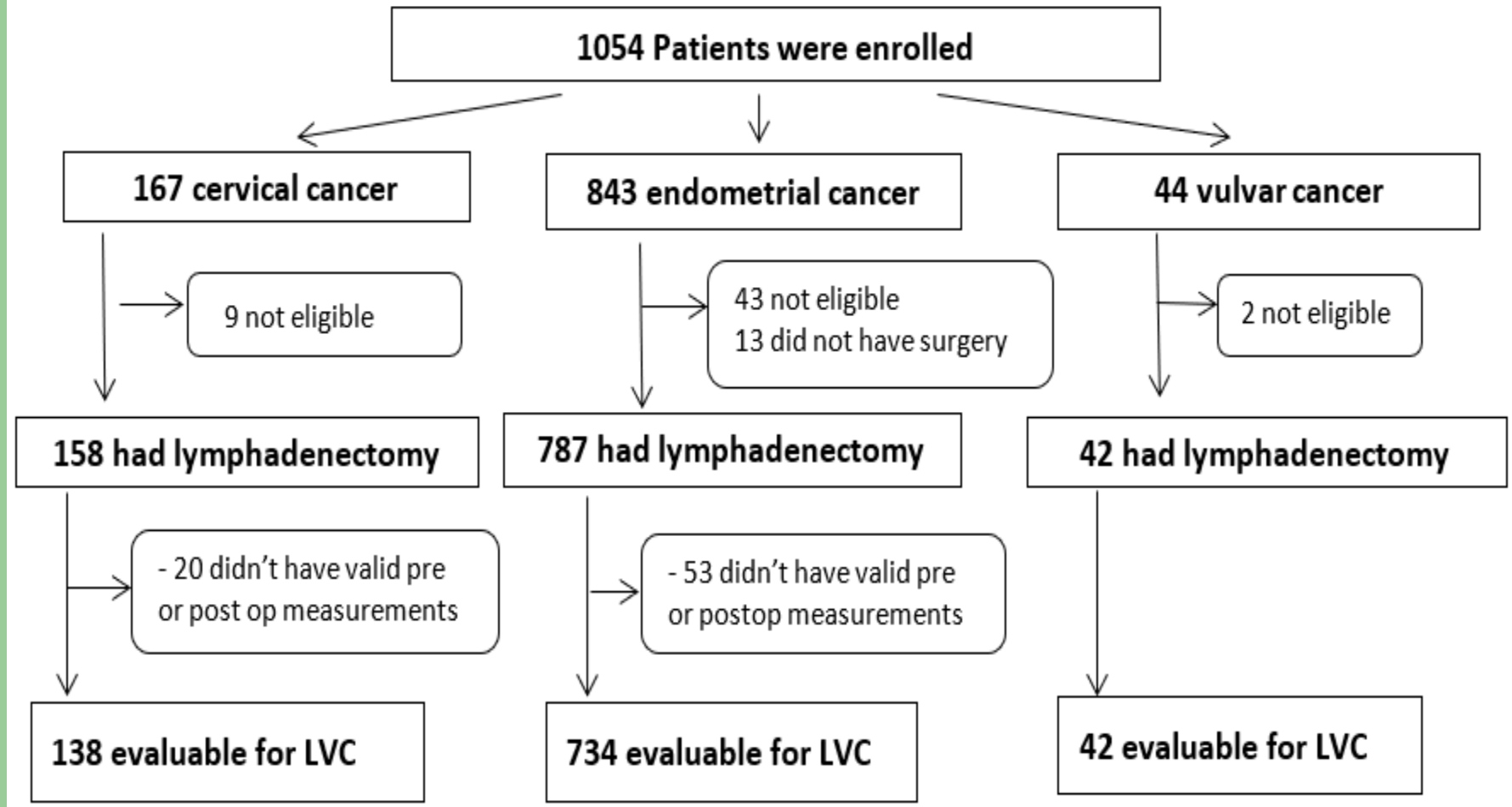
Methods: Gynecologic Cancer Lymphedema Questionnaire (GCLQ):

- 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

Characteristic Total N=821	Category	Endometrial (n=672)	Cervical (n=124)	Vulvar (n=25)
Age	Mean (range)	X =61 years (28-91)	X = 46 yrs (25-83)	X=59 yrs (35-88)
Race	White Black Asian Other/Unspecif	82% (n=551) 10% (n=64) 3% (n=17) 6% (n=40)	73% (n=90) 5% (n=6) 8% (n=10) 15% (n=18)	88% (n=22) 4% (n=1) ---------- 8% (n=2)
Ethnicity	Non-Hispanic Hispanic Other/Unspecif	93% (n=628) 5% (n=33) 2% (n=11)	82% (n=102) 15% (n=19) 2% (n=3)	92% (n=23) 8% (n=2) ----------
Stage of Disease	Stage I Stage II Stage III Stage IV	80% (n=540) 5% (n=36) 13% (n=89) 1% (n=7)	98% (n=122) 2% (n=2) ---------- ----------	64% (n=16) 12% (n=3) 20% (n=5) 4% (n=1)

GOG 244


1054 Patients were enrolled
167 cervical cancer
843 endometrial cancer
44 vulvar cancer
9 not eligible
43 not eligible
13 did not have surgery
2 not eligible
158 had lymphadenectomy
787 had lymphadenectomy
42 had lymphadenectomy
- 20 didn't have valid pre or post op measurements
- 53 didn't have valid pre or postop measurements
138 evaluable for LVC
734 evaluable for LVC
42 evaluable for LVC

Results GOG 244: LeG Study

Leg Volume Change: Uncensored

LVC	Cervical n=138	Endometrial n=734	Vulvar n=42
> 10%	35% (48)	34% (246)	43% (18)
> 15%	25% (35)	19% (140)	19% (8)
> 20%	12% (17)	11% (79)	14% (6)

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**

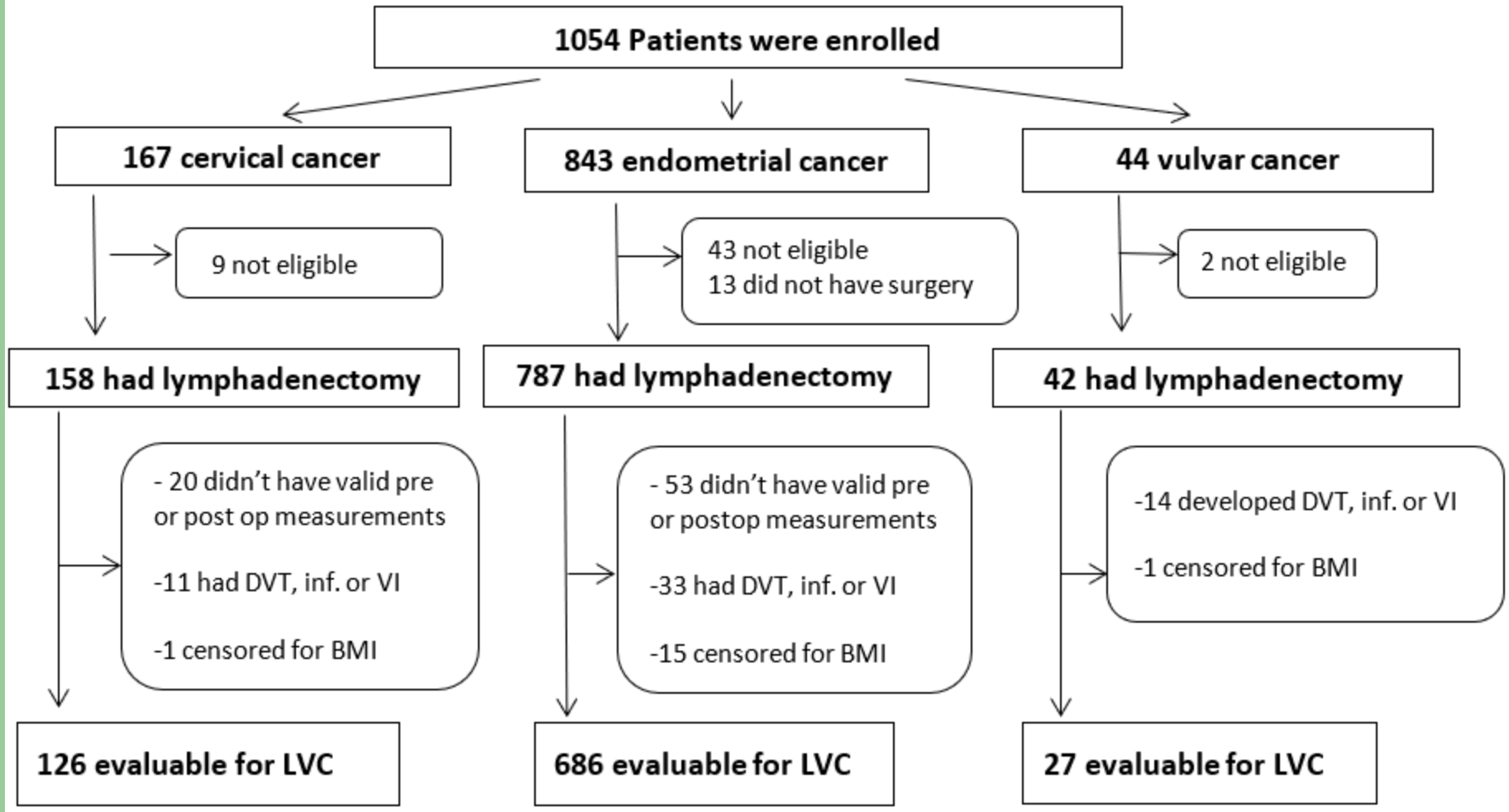
- Due to concerns about measurement error and potential confounding factors, the following steps were taken to ensure identifying true LLE:
  - Patients with DVTs, surgical infection, or vascular insufficiency were removed,
  - BMI ≥10% increase was censored within this analysis
  - Based on GCLQ's ability 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

	Cervical	Endometrial	Vulvar
Vascular Insufficiency (VI)		3 (0.4%)	1 (2.38%)
Infection	9 (6.5%)	22 (3%)	11 (26%)
VTE	1 (0.7%)	4 (0.54%)	2 (4.75%)
Infection + VI		1 (0.14%)	
Infection + VTE		2 (0.27%)	
VTE + VI	1 (0.7%)	1 (0.14%)	
BMI >10%	1	15	1
Totals	12	48	15

GOG 244: Censored data



Results GOG 244: LeG Study

Limb Volume Change: Censored Medical Dx and BMI

LVC	Cervical n=126	Endometrial n=686	Vulvar n=27
> 10%	43 (34.1%)	231 (33.7%)	11 (40.7%)
> 15%	31 (24.6%)	131 (19.1%)	5 (18.5%)
> 20%	13 (10.3%)	75 (10.9%)	3 (11.1%)

Results GOG 244: LeG Study

Data concerns: Lost to follow up

	Cervical	Endometrial	Vulvar
Baseline	138	734	42
Postop	124	669	38
3 months	103	576	30
6 months	104	543	34
9 months	91	504	31
12 months	88	512	29
18 months	83	448	21
24 months	66 (48%)	400 (54%)	17 (40%)

Results: GCLQ Compliance Rates

GCLQ Assessment Time Point	%
Baseline	98%
6 weeks	93%
3 months	83%
6 months	81%
9 months	74%
12 months	74%
18 months	67%
24 months	62%

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 ≥10% combined with GCLQ increase (≥4 points) from baseline in patients without a formal LLE diagnosis

GOG 244: OTHER FINDINGS

Onset of True Lymphedema

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

95% occurred in the first year of follow up

Results: Surgical Approach

Endometrial Cancer: No difference in LLE vs approach

Surgical Approach	Lymphedema Present	Lymphedema Absent	Total N=672
Robotic	348 (63.9%)	74 (58.3%)	422 (62.8%)
Laparoscopic	92 (16.9%)	21 (16.5%)	113 (16.8%)
Open	105 (19.3%)	32 (25.2%)	137 (20.4%)

Results: Surgical Approach

Cervical Cancer : No difference in LLE vs approach

Surgical Approach	Lymphedema Present	Lymphedema Absent	Total N=672
Robotic	45 (50.6%)	14 (45.2%)	59 (49.2%)
Laparoscopic	17 (19.1%)	5 (16.1%)	22 (18.3%)
Open	27 (30.3%)	12 (38.7%)	39 (32.5%)

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

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