



### Lymphedema of the lower limbs after surgery of gynecological cancer



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# The authors have no conflict of interest to declare





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# What do we know about lymphedema and what is the challenge?





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Lymphedema is not a new phenomenon; it was described by the ancient Egyptians in 2000 BC

The historical exploration of the lymphatic system is old, but it was not until the twentieth century that the function of the lymphatics and their pathology were revealed





Ancient Egyptian statue of Pharaoh Mentuhotep II. Egyptian Museum, Cairo. Wikimedia Commons; reprinted by the license <u>CC</u> <u>BY-SA</u>





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The most common reasons for lymphedema in developed countries are secondary lymphedema, secondary to cancer treatment, mainly caused by **disruption of the lymphatic system** by **lymphadenectomy** or **radiation therapy**.

**Stage 0**: The transport of fluid becomes insufficient and is disturbed. The normal physiological transport of lymphatics is blocked

Stage I: The excess fluid in the extracellular space creates swelling

**Stage II**: The stasis of protein rich intracellular fluid and cellular debris causes chronic inflammation.

**Stage III**: This process initiates the proliferation of stromal tissue which is followed by increased adipose deposition and tissue fibrosis\*

\*Executive Committee of the International Society of Lymphology 2020





- The lymphatic system plays an important role in the immune response.
- Injury to the lymphatic systems results in a chronic inflammatory state and activation of the immune system\*.
- The activation of the immune system leads to lymph angiogenesis and chronic inflammation via various immune cells, cytokines, and growth factors.



\*Saito Y, Nakagasmi H, Kaneda Y, et al. Lymphedema and therapeutic lymphangiogenesis. Biomed Res Int. 2013;2013:804675

Schematic diagram of the pathophysiology of lymphedema





The proposed pathophysiology of secondary lymphedema

\*Kataru RP, Baik JE, Park HJ, et al. Regulation of immune

function by lymphatic system in lymphedema. Front Immunol. 2019;10:470.



#### Lymphedema after gynecological cancer treatment.

- Surgery is a cornerstone in the treatment of gynecological cancer.
- In addition to removing the affected gynecological organs, the surgery often includes lymphadenectomy in order to establish a correct staging of the cancer.
- Sentinel node is introduced in vulvar and endometrial cancer.
- Correct surgical staging is important for prediction of prognosis and for tailoring the adjuvant treatment.
- In gynecologic cancer, lymphadenectomy is associated with the development of lymphedema of the lower limbs, in the genital area and impaired health-related quality of life (HRQoL) that may be seen even in early stages of lymphedema.



#### Prevalence of lower limb lymphedema following treatment for gynecological cancer\*

Lymhadenectomy Sentinel Node

Vulvar cancer	10-73%	1.9%
Endometrial cancer	1.2-47%	1.8%
Cervical cancer	10-41%	8.7%
Ovarian cancer	4.7-30.4%	-

\*Dessources K, Aviki E, Leitao MM Jr. Lower extremity lymphedema in patients with gynecologic malignancies. Int J Gynecol Cancer. 2020 Feb;30(2):252-260.

#### Complications of lymphedema\*



• <u>Skin changes</u>; Can be treated with sclerotherapy, CO<sub>2</sub> -laser, surgical resection.



- <u>Pain</u>; Lymphedema is in general not associated with pain.
- <u>Malignancy</u>; Chronic lymphedema can develop into malignant lymphangiosarcoma. Risk ~0.07
- <u>Heart failure</u>; Severe lymphedema may cause heart failure.





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#### Treatment of lymphedema\*

- <u>Self Care</u>; Skincare Avoid obesity and trauma (infection risk)
- <u>Compression</u>; The purpose is to avoid capillary leakage. Regular check-ups.
- <u>Pneumatic compression</u>; Intermittent pressure. Is less effective in higher stages of lymphedema when fibrosis has developed.
- <u>Surgery;</u>
  - -Lymphatic vessel transplantation –anastomose graft is reimplanted (Experimental)
  - -Lymphatic –venous anastomosis (Experimental)
  - -Reimplantation of lymph nodes (Experimental)
  - -Lipectomy-suction: Treatment of severe stages not respondings to conservative treatment.

Assessing Lymphedema; What is the challenge?





- There is no `Gold standard` method for assessing lymphedema.
- The literature reports a wide range of methods for determine lymphedema.
- Baseline assessment are mostly missing.

Method of assessment	Reference number
Method of LLL determination not described	15,18,35,36,49,50,52,53,55,60
Baseline assessment performed	19
Objective measurement of lower limb	6,19,24
Using systematic clinical grading system.	
ISL	6,21,24,27-29
NCI-CTC	20,22,31,32
National Lymphedema Network	16
Evaluation by lymphedema management specialist	9
Radiology method (MRI, ultrasound)	24,43
Validated lymphedema specific questionnaire	7,34,37,40,43-48,57-59
Reported in medical record as patient complaint and/or doctors clinical evaluation	8,16,23,38,39,41-43,51,54,56
Subjective report from patient	9,10,12,17,39,46

\*Lindqvist E, Wedin M, Fredrikson M, Kjølhede P. Lymphedema after treatment for endometrial cancer - A review of prevalence and risk factors. Eur J Obstet Gynecol Reprod Biol. 2017 Apr;211:112-121.



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#### On the Impact of Lymphadenectomy and Lymphedema after Surgery for Endometrial Cancer

longitudinal observational multicenter study

#### The LASEC trial Lymphedema After Surgery of Endometrial Cancer

260 women with presumed early stage endometrialcancer (FIGO stage I-II) were included.235 completed the study.

Patients were evaluated and treated according to the Swedish National Guidelines for Endometrial Cancer.

n = 116 + Lymphadenectomyn = 119 - Lymphadenectomy





#### Evaluation of patients on four occasions;

Preoperatively, 4-6 weeks, 6 months, and one year postoperatively.

• Systematic circumference measurement of the legs enabling calculation of leg volume\*.



• Clinical evaluation and grading of lymphedema #.

• Quality of life questionnaires: SF-36, EQ-5D-3L and LYMQOL §.

\*Sitzia J. Volume measurement in lymphedema treatment: examination of formulae. Eur J Cancer Care 1995;4(1):11-16.

# Bruna J, Miller AJ, Beninson J. A simple clinical classification of lymphedema. Eur J Plast Surg. 1999;22:404-5.

§ Keeley V, Crooks S, Locke J et al. A Quality of life measure for limb lymphedema (LYMQOL). J Lymphoedema. 2010;5(1):26-37.

#### **Results the LASEC trial**



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- The incidence of lymphedema varied between 9.5% and 29.6%, depending on the method of assessing lymphedema \*
- Risk factors for lymphedema are not concordant when assessed by using different methods of determining lymphedema #
- Lymphadenectomy, age, diabetes mellitus and adjuvant radiation seemed to be independent risk factors for lymphedema <sup>#</sup>
- Lymphedema-specific HRQoL (LYMQOL) showed impaired quality of life §

Incidence and risk factors for lymphedema						
	Method					
Incidence of	Volume increase ≥10%	Volume increase ≥10% BMI adjusted volym	Clinical grading	Patient-perceived swelling		
lymphedema	12,1 % (28/231)	9.5% (22/231)	17.5% (40/229)	29.6 % (68/230)		
Risk factors pre-, per- och postoperatively	Lower BMI Diuretics	Age Diabetes mellitus Lymphadenectomy Adjuvant RT	Lymphadenectomy	Age, BMI Lymphadenectomy, Clavien-Dindo grade >3.		

\*Wedin M, et al; LASEC study group. Incidence of lymphedema in the lower limbs and lymphocyst formation within one year of surgery for endometrial cancer: A prospective longitudinal multicenter study. Gynecol Oncol. 2020 Oct;159(1):201-208.

# Wedin M, et al. Risk factors for lymphedema and method of assessment in endometrial cancer: a prospective longitudinal multicenter study. Int J Gynecol Cancer. 2021 Nov;31(11):1416-1427. § Wedin M, et al. Impact of lymphadenectomy and lymphoedema on health-related quality of life 1 year after surgery for endometrial cancer. A prospective longitudinal multicentre study. BJOG. 2022 Feb;129(3):450-460.

#### **Results the LASEC trial**



• Lymphedema or not - depends on the method used for assessing lymphedema.

• There is a need for `gold standard` for assessing lymphedema in a clinical and scientific context – **This is the challenge!** 



## Thank you,

to all women who participated in the study and to all the co-workers in the LASEC trial

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