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S2k Guideline

‘Diagnostics and therapy of lymphoedema’

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Working group 1: Definition and epidemiology

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1. Definition of lymphoedema

Lymphoedema is a chronic inflammatory disease of the interstitium, which results from primary (congenital) or secondary (acquired) damage to the lymphatic drainage system (Table 1), thus to initial lymphatic vessels (lymphatic capillaries and sinuses), precollectors, lymphatic collectors, lymphatic ducts or lymph nodes. Also see: *The diagnosis and treatment of peripheral lymphoedema: 2013 Consensus Document of the International Society of Lymphology* (Lymphology 2013; 46:1-11). Under physiological conditions, there is equilibrium between the tissue fluid filtered (but not reabsorbed) into the interstitium through the blood vessel walls (lymphatic obligatory load) and its removal from the interstitium (transport capacity of the lymphatic drainage system). Insufficiency of the lymphatic drainage system consecutively increases and changes tissue fluid. The further course of the disease is marked by tissue alterations independent of the anatomical site (1). Because lymphoedema is per se suspected to be carcinogenic, the term 'malignant lymphoedema' should be mentioned in this context. It is important to keep in mind that lymphatic drainage may be severely impaired by *lymphangiosis carcinomatosa* (invasion of lymphatic vessels by tumour cells) and by tumour invasion of lymph nodes.

Table 1: Causes of primary and secondary lymphoedema

Primary lymphoedema	Secondary lymphoedema
	Surgery
	Lymphadenectomy
Aplasia/atresia	Irradiation
Hypoplasia	Malignant processes
Hyperplasia/dysplasia	Traumatic/posttraumatic (scars)
Lymph node fibrosis	Post-/infection
Lymph node agenesis	Obesity
	Advanced stages of chronic venous insufficiency (CVI)
	Deliberate induction

Primary lymphoedema is associated with genetic disposition and either caused by gene mutations inherited via the germline or by sporadically occurring gene mutations. Such mutations can already be present in foetuses or new-borns but may also become noticeable many years later (2). The mutations of several genes are known to cause lymphoedema, and 9 of these genes are summarised in Table 2. Lymphoedema is often part of complex

congenital syndromes associated with gigantism, for instance of the extremities (3). Traditionally, such syndromes are named after the first person to describe the disease, for instance Klippel-Trénaunay-Weber syndrome or Turner syndrome. However, research into the genetic causes is increasing. Several gene defects are presently being evaluated in German-speaking countries (see also: 'Das Humangenetische Qualitätsnetzwerk' [Human Genetics Quality Network]; http://www.hgqn.eu/).

Table 2: Genetic causes of primary lymphoedema

OMIM	Disease	Gene locus	Gene	Molecule/ mutation	Reference
#153100	Primary congenital lymphoedema, Nonne-Milroy	5q35.3	FLT4 = VEGFR-3	Mutations of the tyrosine kinase domain	(4)
#153400	Lymphoedema distichiasis, also includes lymphoedema ptosis and yellow-nail syndrome	16q24.3	FOXC2	Winged-helix transcription factor, Nonsense or Frameshift mutation	(5) (6)
#615907	Similar to Milroy disease	16q24.3	VEGF-C	Growth factor	(7)
#613480	Lymphoedema of the arms and legs	1q41-42	GJC2	Connexin 47	(8)
#614038	Lymphoedema of the legs and the genitals	3q21	GATA2	Transcription factor	(9)
#607823	Hypotrichosis lymphoedema telangiectasia syndrome	20q13.33	SOX18	SRY-type HMG-box transcription factor, Missense mutation	(10)
#613611	Lymphoedema of the legs and atresia of the choanae	1q41	PTPN14	Protein tyrosine phosphatase (non−receptor type)	(11)
#235510	Hennekam syndrome	18q21	CCBE1	Secreted protein	(12)
#152950	Microcephalia, lymphoedema and chorioretinopathy	10q23.33	KIF11	Motor protein	(13)

Secondary lymphoedema may be caused by various diseases and injuries or result from therapeutic intervention. Possible causes are extirpation of axillary lymph nodes after breast carcinoma (14) but also excision of pelvic, para-aortal, inguinal and femoral lymph nodes (15, 16) or neck dissection (17).

Untreated lymphoedema constitutes a chronic progressive disease marked by consecutive increase and changes in tissue fluid and the extracellular matrix (ground substance). It should be noted that tissue fluid is not only an ultrafiltrate of blood but also responsible for removing proteins secreted by specific organs and tissues (18). The further course of the disease is marked by trophic dysfunction of tissues and organs in association with an increase in connective tissue (fibrosis and sclerosis) and fatty tissue as well as changes in the composition of the extracellular matrix (types of collagen, elastin and glycosaminoglycans such as hyaluronan) (19).

Impaired lymphatic flow also disrupts the circulation of leukocytes (lymphatic fluid contains the following cell types: T lymphocytes (80%), Langerhans cells (6-10%), monocytes (2-8%), and B lymphocytes (1-4%). Lymphoedematous tissue also facilitates acute infections such as erysipelas (termed cellulitis in Anglo-American regions), an acute inflammatory group A streptococcal dermatitis (20, 21).

Differentiation from other forms of oedema

Oedema (enlargement of the intercellular space mostly as a result of increased interstitial fluid volume) may be a symptom of a wide range of diseases, for instance cardiac, renal, hepatic, endocrine, drug-induced and infectious or oncotic diseases. Oedema should not be confused with lymphoedema, which is a disease / insufficiency of the lymphatic drainage system. Lymphoedema is marked by insufficient drainage of the interstitium via the lymphatics. Thereby, increased influx (filtration) of fluid from blood vessels into the interstitium can aggravate the disease. Oedema can be generalised or local and may be painful or painless. Mixed forms of oedema and lymphoedema have been reported.

2. Epidemiology of lymphoedema

The incidence of primary lymphoedema at birth is estimated to be 1:6,000 (22), and its prevalence among the under 20 year-olds is approximately 1:87,000 (23).

Exact figures of the incidence of secondary lymphoedema are difficult to determine, and causes vary widely from country to country. In industrialised countries, the incidence of secondary lymphoedema is assumed to range between 0.13% and 2.00%. In England (about 50 million inhabitants), lymphoedema has been diagnosed in about 100,000 people (24). Women are significantly more often affected by primary lymphoedema than men; the ratio of men to women ranges between 1:4.5 (24, 25) and 1:6.1 (26). The number of affected patients increases with age. The most common cause of secondary lymphoedema in industrialised countries is malignant tumours and their treatment. The excision of lymph nodes in the inguinal region more often results in lymphoedema than the excision of axillary lymph nodes (25). Figures for patients with cancer who develop lymphoedema vary widely (27). However, the situation has obviously been improved by advanced surgical techniques

over the past few years. The incidence of lymphoedema 12 to 24 months after the excision of axillary lymph nodes because of breast carcinoma is 19.9% and 5.6% after sentinel node biopsy (28). The incidence of lymphoedema after the excision of lymph nodes because of gynaecological tumours is about 20% (17, 29, 30). However, some studies have yielded percentages of 47 (31) and 60 (32) after specific gynaecological surgical procedures. The fact that the development of lymphoedema is induced and aggravated by obesity is epidemiologically significant (33, 34).

3. Stages of lymphoedema

The following stages of lymphoedema need to be differentiated:

Stage of latency Stage 0 Subclinical stage	No clinically visible lymphoedema but sometimes pathological scintigraphic findings
Stage I (spontaneously reversible)	Oedema of soft consistency, swelling reduced by elevation of the limb
Stage II (not spontaneously reversible)	Oedema with secondary tissue alterations; swelling not reduced by elevation of the limb
Stage III	Hard distorted swelling, partly lobar and partly with typical skin alterations

4. Pathophysiology of lymphoedema

Lymphoedema is a disease which induces the formation of oedema in the interstitium.
Two key mechanisms result in the formation of interstitial oedema:

1. Unphysiologically high influx of fluid from blood vessels into the interstitium,
2. Insufficient efflux of interstitial fluid via blood or lymphatic vessels or both.

Traditionally, two types of lymphoedema were differentiated: low protein oedema and high protein oedema.

Low protein oedema:
If the natural barrier function of the endothelial cells of the blood vessels remains intact, low protein oedema develops, which can be deeply pressed with a finger (pitting oedema). Low protein oedema is a symptom of another underlying disease.

High protein oedema:
High protein oedema develops in the case of defective natural barrier function of the endothelial cells of the blood vessels or if lymphoedema has developed. At its advanced stages, high protein oedema can no longer be pressed with a finger (non-pitting oedema).

However, the basis of protein richness differs between these two types of lymphoedema. Lymphoedema is marked by a typical sequence of tissue alterations, which mainly develop in the intercellular space (interstitial space) and in the cells controlling this space. In animal experiments on primary lymphoedema, increased colloid osmotic pressure has been measured in the interstitium as a sign of increasing protein concentration (35). In this case, intercellular fluid shows organ-specific differences. However, the question which molecules regulate subsequent changes in the interstitium has hardly been investigated so far.

Changes in cells and in the intercellular space in lymphoedema

Lymphoedema of the skin is associated with the following changes: The initial stage I is marked by an increase in free interstitial fluid. The advanced stages II and III are associated with the following symptoms:

1. Thickened cutis and subcutis due to
    a. Accumulation of fatty tissue,
    b. Increase in connective tissue (fibrosis and sclerosis),
    c. Development of lymphatic cysts (chylous cysts) and fistulae.
2. Trophic changes in the epidermis:
    a. Hyperplasia and hyperkeratosis,
    b. Discolouration of the skin (hyperpigmentation),
    c. Minor papillomatosis,
    d. Verrucous protuberances (‘elephant skin’).
3. Abnormal immune response:
    a. Susceptibility to erysipelas,
    b. Susceptibility to mycotic infection,
    c. Others.
4. Painful changes in the musculoskeletal system.

Changes in the intercellular space

In lymphoedema, molecular changes in the intercellular space are still inadequately investigated. In the initial stage of lymphoedema, tissue shows higher transparency and reduced histological dyeability (36), probably due to the increased retention of water-binding hyaluronan (19). Stages II and III are marked by an increased number of fibres in the interstitium (36). Immunohistological examinations have shown collagen type I and type III, resulting in a significant increase in the thickness of the corium. Some areas show clearly recognisable fibres and other areas amorphous substances (such as fibronectin and albumin), but the other substances remain largely unclear. The diameter of collagenous fibres increases to 40-400 nm in contrast to 25-200 nm in normal skin, and more long-spacing collagen can be found showing cross-striations of 80-120 nm periodicity (instead of 64 nm) (37). Changes in the basal membranes (discontinuities) can be shown by means of electron microscopy. Often, basal laminae have become detached from the endothelium of the blood vessels. A dense matrix resembling basal lamina develops around lymphatic capillaries. It is not yet known if this process involves changes in the elastic fibre networks and the anchoring filaments. Immunohistological examinations have yielded matrix

metalloproteinases (MMPs), which break down the different matrix components, but their activity has not yet been investigated. The area of lymphatic collectors has not only shown hyperplasia of muscles but also an increase in the content of fibres (36).

Changes in the extracellular matrix may be regulated by the transforming growth factor β (TGF-β) secreted by dendritic cells. In this context, TGF-β may work in two ways: first as an inhibitor of the formation of lymphatic vessels (lymphangiogenesis) and, second, as an activator of scar formation and fibrosis (38).

Changes at the cellular level

At the initial stage of lymphoedema, most changes are likely to develop in local cells (pre-adipocytes, fibrocytes, resident macrophages and mast cells), whereas stages II and III are marked by an increase in the number of cells in the tissue (36). Other characteristics are the massive development of adipocytes and the increase in the number of fibroblasts. The transdifferentiation of fibroblasts into myofibroblasts has been the subject of controversial debate (36, 37). Cells presenting on lymphatic capillaries have been interpreted as pericytes (37).

CD68-positive macrophages can often be detected, which obviously phagocytose collagen fibres. The number of CD34-positive cells is rather high (36). This transmembrane glycoprotein is expressed in a sub-population of dendritic cells, haematopoietic progenitor cells, endothelial cells of blood vessels (rarely of lymphatic cells) and mast cells. The number of factor XIIIa-positive dendritic cells is significantly increased. Thus, not only the number of infiltrating macrophages is increased but also the number of resident macrophages or antigen-presenting cells. Resident macrophages proliferate during a period termed pre-chronical phase. These cells produce a wide range of cytokines and growth factors. No signs of granulomatous inflammation can be found (36).

The question which molecular factors are responsible for the massive development of adipose tissue during lymphostasis has never been investigated. Interactions between the immune system and the adipose tissue – similar to those in Crohn's disease and acquired immune deficiency syndrome (39) – seem possible.

The number of lymphatic vessels in the different stages of lymphoedema has not yet been investigated. Only data obtained from animal experiments are available, but these findings date back to the times in which immunohistological identification of lymphatic vessels was not yet possible (40). The question whether the reported relative increase in lymphatic capillaries with regard to volume and length also occurs here requires further clarification. Lymphatic collectors have been reported to react with muscle hypertrophy and fibrosis (41). The advanced stages of lymphoedema show evidence of fibrosis of lymph nodes and afferent lymphatic collectors (36).

5. Molecular basics of primary lymphoedema

Primary lymphoedema presumably only accounts for about 1% of all lymphoedema (42-44); thus, the absolute number of patients affected worldwide may be rather high. Patients (who wish to have children) may not only be interested in the mode of inheritance of the underlying gene defect but also in the availability of a specific causal therapy. Both human genetic diagnostics as well as genetic counselling of patients would be desirable. No causal therapy is yet available; however, such therapies should not be fundamentally ruled out because several mechanisms regulating the structure and function of lymphatic vessels are already known.

Genetic diagnostics (for instance by exome sequencing) usually focus on genes whose mutations have already been explicitly linked to the development of lymphoedema. Extremely rare mutations are negligible, so that − according to the current state of knowledge − diagnostics can be focused on the following 9 genes (see also Table 2):

Hereditary lymphoedema I-A (Nonne-Milroy lymphoedema)
Gene: *FLT4* = *VEGFR-3*; OMIM (Online Mendalian Inheritance in Man) no.: 153100. The FLT4 gene is located on chromosome 5q35.3 and encodes the vascular endothelial growth factor receptor-3 (VEGFR-3). Heterozygote mutations in the *VEGFR-3* gene are probably the cause of the majority of primary lymphoedema (45). These mutations become noticeable when they affect the function of the domain of the receptor tyrosine kinase (4, 8, 46).

Hereditary lymphoedema I-D
Gene: *VEGF-C*; OMIM no.: 615907. VEGF-C is the most important growth factor in lymphangiogenesis (47). Mutations affecting the secretion and receptor affinity of the factor lead to the development of congenital or childhood lymphoedema of the legs, similar to that of Nonne-Milroy lymphoedema (7).

Lymphoedema-distichiasis syndrome
Gene: *FOXC2*; OMIM no.: 153400. The *FOXC2* gene is located on chromosome 16q24.1 and encodes the transcription factor FOXC2. Transcription factors regulate the expression of a wide range of genes. Mutations of the most important transcription activation domain of the FOXC2 gene lead to lymphoedema of the legs and, simultaneously, to the formation of a double row of eyelashes (distichiasis) (6). Apart from lymphoedema of the legs, many patients also develop venous reflux in the great saphenous vein and varicosities because FOXC2 regulates the formation of valves in the lymphatic collectors as well as in the veins (48).

Hereditary lymphoedema I-C
Gene: *GJC2*; OMIM no.: 613480. The *GJC2* gene is located on chromosome 1q41-q42 and encodes the gap junction protein Gamma2 (Connexin 47; CX47). Connexins are transmembrane proteins; as hemi-channels, they connect two cells in the form of gap

junctions, thus enabling the exchange of ions and low molecules. Mutations in the *GJC2* gene were found in several families with lymphoedema of the arms or legs (development of lymphoedema between the ages of 1 and 40) (8, 49).

Hypotrichosis-lymphoedema-telangiectasia syndrome (HLTS)

Gene: *SOX18*; OMIM no.: 607823. The *SOX18* gene is located on chromosome 20q13.33 and encodes a DNA-binding transcription factor of the SRY family. HLTS is a complex disease which is associated with early hair loss in connection with ectatic blood vessels and lymphoedema. Mutations in the *SOX18* gene were found in 3 families affected by HLTS (10), whose members developed lymphoedema of the legs at the age of 15 years or already at the age of 4 years (50).

Choanal atresia and lymphoedema

Gene: *PTPN14*; OMIM no.: 613611. The *PTPN14* gene is located on chromosome 1q41 and encodes protein tyrosine phosphatase of the non-receptor type. Protein tyrosine phosphatase catalyses the removal of phosphate groups from phosphorylated proteins. PTPN14 binds to VEGFR-3, thereby decreasing the activity of this receptor (51). Mutations destroying the catalytic activity of PTPN14 effect the development of childhood lymphoedema and choanal atresia (11).

Microcephaly with or without chorioretinopathy, lymphoedema or mental retardation

Gene: *KIF11*; OMIM no.: 152950. The *KIF11* gene is located on chromosome 10q23 and encodes a motor protein of the kinesin family. KIF11 (also termed Eg5) is essential for transporting chromosomes along the microtubules of the mitotic spindle during cell division (52). KIF11 is highly expressed in blood and lymph endothelial cells and regulates angiogenesis (53). Total loss of KIF11 function is not compatible with life (54). Mutations of the KIF11 gene cause a multitude of serious defects as well as lymphoedema on the back of the foot, which is either already present at birth or develops shortly afterwards (13).

Primary lymphoedema with myelodysplasia (Emberger syndrome)

Gene: *GATA2*; OMIM no.: 614038. The *GATA2* gene is located on chromosome 3q21 and encodes a transcription factor which – next to the development of blood cells − also controls the function of lymphatic vessels in a hitherto unknown manner. The Emberger syndrome is often characterised by congenital dysplasia in the face. In childhood or early adulthood, patients develop lymphoedema of the legs and often also genital lymphoedema, pancytopenia or acute myeloid leukaemia (9, 55).

Hennekam lymphangiectasia-lymphoedema syndrome

Gene: *CCBE1*; OMIM no.: 235510. Hennekam syndrome is a rare condition, which is caused by mutations in the *CCBE1* gene on chromosome 18q21.32 and marked by malformation of the intestinal lymphatic vessels (intestinal lymphangiectasia) (12, 56). In addition, malformations of the lymphatic vessels develop on the trunk of the body, the face, the genitals as well as on the arms and legs. This type of lymphoedema becomes

disproportionately large. Intestinal lymphangiectasia is associated with hypoproteinaemia, hypogamma-globulinaemia and lymphocytopenia, which not only facilitate the development of massive lymphoedema but also complicate therapy. In addition to lymphoedema, cerebral dysfunctions develop together with mental retardation, facial abnormalities, tooth deformities and ear defects.

6. Differentiation from obesity and lipoedema

Obesity

Obesity is a major risk factor for the development of secondary lymphoedema, which is probably caused by mechanical impediment of the lymph transport (14, 57). Obesity is the accumulation of fat cells (adipocytes) beyond the normal level. Apart from internal organs, adipocytes mainly develop in the subcutis. Calculation is based on the body mass index (BMI), which is derived from a person's body mass (weight in kilogrammes) divided by the height^2 (in meters); BMI = m:l^2. Further important factors are age, sex and fat distribution. See also the guidelines of the Association of the Scientific Medical Societies in Germany: Therapy of obesity in children and adolescents (http://www.awmf.org/leitlinien/detail/ll/050-002.html); Obesity – Prevention and therapy (http://www.awmf.org/leitlinien/detail/ll/050-002.html); Inpatient rehabilitation of obesity (http://www.awmf.org/leitlinien/detail/ll/070-001.html); Surgery of obesity (http://www.awmf.org/leitlinien/detail/ll/088-001.html).

When a patient presents with both obesity and lymphoedema, the acute focus is on lymphological aspects; however, obesity should be viewed as primary disease and lymphoedema as secondary disease.

Lipoedema

Lipoedema is the symmetrical accumulation of fatty tissue, which is characterised by its susceptibility to haematoma and its sensitivity to pressure and pain. Lipoedema mainly develops below the iliac crest (hips and thighs) (58). Primarily, the lymphatic drainage system is not involved. At the advanced stage III, lipoedema may develop into lymphoedema (59, 60). For the definition of lipoedema, see also the guideline of the Association of the Scientific Medical Societies in Germany (http://www.awmf.org/uploads/tx_szleitlinien/037-012l_S1_Lipoedem_2016-01.pdf).

The aetiology of lipoedema is still unclear. A hereditary connection seems likely. Lipoedema is marked by the dysfunctional distribution of fatty tissue and mainly affects women. The hormonal involvement in the aetiology of the disease is reflected in the fact that the onset of lipoedema mainly occurs at the beginning of puberty, sometimes after pregnancy or during menopause (59). In the presence of both lipoedema and lymphoedema, the acute focus is on lymphological aspects.

7. ICD 10-codification of lymphoedema

Since 2017, the German modification of ICD-10 (ICD-10-GM) allows the codification of lymphological diseases according to the body site and, to a large extent, to the different disease stages. Although such differentiation requires more time in daily clinical practice, all physicians involved in lymphological treatment should use this opportunity to exactly describe the extent of treatment required at the different disease stages. The classification system may be downloaded at the website of the German Institute of Medical Documentation and Information (DIMDI) (http://www.dimdi.de/static/de/index.html).

First of all, hereditary lymphoedema has to be differentiated from other types of lymphoedema, such as secondary lymphoedema after surgery or other medical treatment, in rare cases also sporadically (primary, non-hereditary) (Fig. 1).

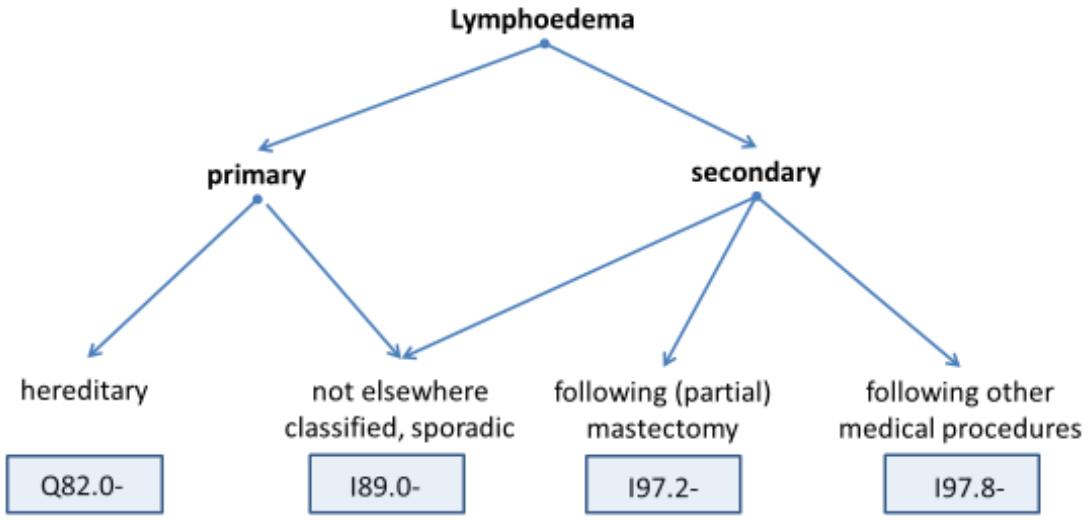

Figure 1: Classification system of lymphoedema

The following list contains the correct codes for primary non-hereditary lymphoedema (I89.0-), secondary lymphoedema (I89.0-) and hereditary lymphoedema (Q82.0-). Primary non-hereditary and secondary lymphoedema are to be differentiated according to the level of severity. Different codes are available for complications such as lymphatic fistulae, lymphoceles, lymphatic cysts, lymphogenic leg ulcers and lymphogenic ulcers at other body sites as well as erysipelas (cellulitis) (A46). The relevant information has been added (Tables 3 and 4).

I89.- **Other non-infective disorders of lymphatic vessels and lymph nodes**

I89.0- **Lymphoedema, not elsewhere classified**
Lymphangiectasis

Complications such as cutaneous lymphatic fistulae, subcutaneous lymphoceles, dermal lymphatic cysts, chylous reflux (all I89.8) or lymphogenic ulcers (L97, L98.4) need to be coded separately.
Concurrent lipoedema is also to be coded separately (E88.2-).

I89.00 Lymphoedema of the upper and lower extremities, stage I

I89.01 Lymphoedema of the upper and lower extremities, stage II

I89.02 Lymphoedema of the upper and lower extremities, stage III

I89.03 Lymphoedema of other body sites, stage I
Head, neck, thoracic wall and genital area

I89.04 Lymphoedema of other body sites, stage II
Head, neck, thoracic wall and genital area

I89.05 Lymphoedema of other body sites, stage III
Head, neck, thoracic wall and genital area

I89.08 Other lymphoedema, not elsewhere classified
Stage of latency of lymphoedema

I89.09 Lymphoedema, not further specified

Table 3: Classification of non-hereditary primary and secondary lymphoedema (except after medical procedures)

Q82.- Other congenital malformations of skin

Q82.0- Hereditary lymphoedema
Complications such as cutaneous lymphatic fistulae, subcutaneous lymphoceles, dermal lymphatic cysts, chylous reflux (all I89.8) or lymphogenic ulcers (L97, L98.4) need to be coded separately.
Concurrent lipoedema is also to be coded separately (E88.2-).
Excluding: Acquired lymphoedema (I89.0-)
Lymphoedema after (partial) mastectomy (I97.2-)
Lymphoedema after medical procedures, not elsewhere classified (I97.8-)

Q82.00 Hereditary lymphoedema of the upper and lower extremities, stage I

Q82.01	Hereditary lymphoedema of the upper and lower extremities, stage II
Q82.02	Hereditary lymphoedema of the upper and lower extremities, stage III
Q82.03	Hereditary lymphoedema of other body sites, stage I Head, neck, thoracic wall and genital area
Q82.04	Hereditary lymphoedema of other body sites, stage II Head, neck, thoracic wall and genital area
Q82.05	Hereditary lymphoedema of other body sites, stage III Head, neck, thoracic wall and genital area
Q82.08	Other hereditary lymphoedema
Q82.09	Hereditary lymphoedema, not further specified

Table 4: Classification of hereditary lymphoedema

Lymphoedema following mastectomy (I97.2-) may also be coded according to its different stages. This code also includes lymphoedema after axillary dissection or lymph node dissection with partial mastectomy (tumourectomy, lumpectomy and quadrant resection) (Table 5).

I97.-	**Postprocedural disorders of the circulatory system, not elsewhere classified**
I97.2-	**Lymphoedema following (partial) mastectomy** Obliteration of lymphatic vessels due to mastectomy
I97.20	Lymphoedema following (partial) mastectomy (with lymphadenectomy), stage I
I97.21	Lymphoedema following (partial) mastectomy (with lymphadenectomy), stage II
I97.22	Lymphoedema following (partial) mastectomy (with lymphadenectomy), stage III
I97.29	Lymphoedema following (partial) mastectomy (with lymphadenectomy), not further specified

Table 5: Classification of lymphoedema after (partial) mastectomy

Lymphoedema after other medical procedures are coded according to the following body sites: cervical, inguinal, urogenital and others. Codes for the most commonly affected body sites (axillary and inguinal) are to be differentiated according to the stage of lymphoedema (Table 6). These codes also include lymphoedema following surgery of lymph node relapse after previous mastectomy.

I97.8- Other postprocedural disorders of the circulatory system, not elsewhere classified

Complications such as cutaneous lymphatic fistulae, subcutaneous lymphoceles, dermal lymphatic cysts, chylous reflux (all I89.8) or lymphogenic ulcers (L97, L98.4) need to be coded separately.

I97.80 Lymphoedema after medical procedures in the lymphatic drainage area of the neck, all stages

I97.81 Lymphoedema after medical procedures in the lymphatic drainage area of the axilla, stage I

Excluding: Lymphoedema after (partial) mastectomy and axillary lymphadenectomy, stage I (I97.20)

I97.82 Lymphoedema after medical procedures in the lymphatic drainage area of the axilla, stage II

Excluding: Lymphoedema after (partial) mastectomy and axillary lymphadenectomy, stage II (I97.20)

I97.83 Lymphoedema after medical procedures in the lymphatic drainage area of the axilla, stage III

Excluding: Lymphoedema after (partial) mastectomy and axillary lymphadenectomy, stage III (I97.20)

I97.84 Lymphoedema after medical procedures in the lymphatic drainage area of the groin, stage I

I97.85 Lymphoedema after medical procedures in the lymphatic drainage area of the groin, stage II

I97.86 Lymphoedema after medical procedures in the lymphatic drainage area of the groin, stage III

I97.87 Lymphoedema after medical procedures in the urogenital system, all stages

I97.88 Lymphoedema after medical procedures at other body sites, for instance the thoracic wall, all stages

I97.89 Other postprocedural disorders of the circulatory system, not elsewhere classified

Table 6: Classification of lymphoedema after other medical procedures

The different codes for lymphoedema are summarised in Table 7.

Lymphoedema	**Stage 0**	**Stage I**	**Stage II**	**Stage III**	**Not otherwise specified**
Hereditary					
Extremities (upper and lower)	Q82.08	Q82.00	Q82.01	Q82.02	Q82.09
Other body sites (head, neck, thoracic wall and genital area)		Q82.03	Q82.04	Q82.05	
Sporadic / secondary					
Extremities (upper and lower)	I89.08	I89.00	I89.01	I89.02	I89.09
Other body sites (head, neck, thoracic wall and genital area)		I89.03	I89.04	I89.05	
After medical procedures					
(Partial) mastectomy	*I97.29**	I97.20	I97.21	I97.22	I97.29
Cervical	I97.80				
Axillary (except after mastectomy)	*I97.89**	I97.81	I97.82	I97.83	*I97.89**
Inguinal	*I97.89**	I97.84	I97.85	I97.86	*I97.89**
Urogenital (for instance genital area, urinary bladder, prostate, ovaries or uterus)	I97.87				
Other body sites (for instance thoracic wall)	I97.88				

Table 7: Classification of lymphoedema (* more specific codes are not available)

Working group 2: Basic diagnostics

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1. What examinations are the pillars of basic diagnostics and what do they consist of?

The pillars of basic diagnostics are **history taking, inspection and palpation**, which should be conducted in the given order. Use of the checklist for basic diagnostics is recommended.

Consent 100% (strong consent)

Commentary:

History taking should include patients' general medical history as well as their specific history of oedema:

General history taking includes questions on familial predisposition (increased familial prevalence of lymphoedema, vascular diseases or oedema of the legs), surgical interventions (vascular, oncologic, orthopaedic and others), other medical conditions (metabolic and hormonal disorders as well as renal, hepatic or cardiovascular diseases), skin changes, vascular diseases, previous inflammatory processes such as erysipelas/cellulitis, erythema migrans, tick bites and bites by other insects as well as questions about overseas stays (including stays in the tropics) (61). In the case of a medical history of tumour disease: Disease onset, tumour stage, histology, tumour-specific therapy and course of the disease (tumour recurrence?). Further questions include possible immobilisation due to injury and orthopaedic or neurologic diseases. History taking will be completed by additional questions about vegetative history, significant weight fluctuations and intake of medication. Specific history taking of oedema includes questions about temporal disease progression, the primary location and direction of proliferation, complaints and symptoms (swelling, functional limitations in everyday life, pain, susceptibility to hematoma or discharge of tissue liquid), inflammatory secondary diseases and specific lymphological pre-treatments (see also attached checklist). History taking summarises all already established findings and includes questions about patients' general medical history and their specific history of lymphoedema. Furthermore, patients need to be advised to provide all relevant preliminary findings of at least the previous three years.

Inspection serves to assess patients on the basis of their clinical presentation. Patients need to undress for the inspection and will be examined in both the upright and the supine position. During inspection, the site of the swelling will be determined as well as the difference in the circumference and possibly in the length of the two extremities (hemihypertrophy). Furthermore, the skin will be examined with regard to trophic disorders, coloration and changes such as rough skin texture, ectatic lymphatic vessels of the skin,

lymphatic cysts, hyperkeratosis, papillomatosis cutis lymphostatica, deepened natural skin folds, square toe shape, syndactyly, skin changes indicating fungal infection, for instance interdigital skin maceration, skin changes of venous origin (corona phlebectatica paraplantaris, varicosities and blowout phenomenon) as well as potentially malign skin changes generally associated with lymphoedema (61, 67, 68). Additionally, patients are clinically evaluated regarding shortness of breath, sweating and mobility (see also attached checklist).

Visual examination or **palpation** also requires the patients to undress. Palpation involves examination of the lymph nodes including assessment of their size, consistency, ability to be shifted and tenderness on palpation. Palpation of the oedema enables assessment of its consistency (ranging from tender and pasty to firm and elastic to rough and fibrotic to hard and indurated). A further test includes the degree of indentation in the skin after finger pressure ('pitting oedema'); expressible lymphatic cysts will also be examined by means of finger pressure (61). In order to evaluate the presence of hardened tissue, skinfolds are pinched and lifted at the proximal phalanx of the second or third finger or toe (Stemmer's test) but also at other affected body parts (67). In the case of hardened tissue, the skin can hardly or not at all be lifted because of the induration of the dermal and epidermal tissue (67, 69). The thickness of the skin may also be measured with a calliper. Several methods for determining the level of hardening are available (classification according to the aetiology, body site or stage 0 to 3 [61]; LVF system [70]). In the case of a negative result, lymphoedema cannot be excluded when only the level of hardening is taken into consideration. Palpation should also include measuring the skin temperature and assessing active and passive joint flexibility as well as the cardiovascular system including the arterial and venous status (71) (see also attached checklist).

2. The importance of medical experience in basic diagnostics

The procedures of basic diagnostics (history taking, inspection and palpation) should be carried out by every physician without any problems, but the interpretation of the findings depends on a physician's experience in lymphological diseases.

Consent 100% (strong consent)

Commentary:

The procedures of basic diagnostics (history taking, inspection and palpation) are part of the general medical training. However, examination in specialised centres or practices is recommended because the interpretation of the findings depends on the clinical experience in lymphological diseases (61, 72).

3. What questions can be clinically assessed with basic diagnostics?

Basic diagnostics should be sufficient for the clinical assessment of the aetiology, patient-reported outcome as well as the stage and site of lymphoedema.

Consent 100% (strong consent)

Commentary:

Aetiologically, primary lymphoedema is to be differentiated from secondary lymphoedema (see chapter working group 1) (61, 68, 73). Basic diagnostics may yield indications for complex malformation syndromes.

Secondary lymphoedema due to cancer treatment (secondary benign or secondary malign lymphoedema) needs to be differentiated from secondary lymphoedema without a history of tumour disease (chronic secondary lymphoedema).

Patient-reported outcome of lymphoedema
This term describes the symptoms of lymphoedema reported by affected patients themselves which restrict the quality of life in daily routine and work (74, 75). The symptoms may develop individually or in combination. The symptoms of lymphoedema are:

- Swelling,
- Pain,
- Limited function and mobility,
- Feeling of tightness of the skin,
- Feeling of heaviness,
- Feeling of tightness regarding clothing, shoes and jewellery, and
- Skin changes.

These symptoms have been added to the checklist of basic diagnostics under the category history taking to be used in patient interviews. Such data may also be collected by means of validated questionnaires, for instance the quality of life questionnaire of the EORTC (EORTC QLQ-BR23, breast cancer module) in the case of female patients with breast cancer. This questionnaire on symptoms of lymphoedema of the arms and breast is available in 81 languages: www.eortc.be/qol/downloads/QLQC30/select.asp.

Lymphoedema is differentiated according to four clinical **stages**: stage 0 (stage of latency), stage I (spontaneously reversible), stage II (spontaneously irreversible) and stage III (deformation) (61).

Multiple answers are possible with regard to the **site** of lymphoedema, for instance lymphoedema of the legs, lymphoedema of the arms, lymphoedema of the breast, genital lymphoedema, lymphoedema of the upper quadrant, lymphoedema of the lower quadrant

and lymphoedema of the head or neck. The specification of the body site should also include the affected side of the body (61, 70).

After the final clinical evaluation, lymphoedema can be diagnosed by means of basic diagnostics in most patients. Patients, for whom no diagnosis can be made after basic diagnostics, require further examination (see chapter working group 3).

4. When are basic diagnostics a sufficiently safe method for the clinical assessment of lymphoedema and for the start of appropriate treatment?

Basic diagnostics represent a sufficiently safe method of diagnosis if no relevant comorbidities are present and in the case of advanced-stage lymphoedema (>stage II).

Consent 100% (strong consent)

Commentary:

In the absence of any severe co-morbidity, therapy of lymphoedema according to the respective stage may be initiated immediately.

5. When are basic diagnostics <u>not</u> a sufficiently safe method for the clinical assessment of lymphoedema and for the start of appropriate treatment?

Basic diagnostics alone are insufficient in the presence of co-morbidities indicating differential diagnoses, in early-stage lymphoedema, if internal organs are involved, in medical expert reports and if invasive therapy is taken into consideration.

Consent 100% (strong consent)

Commentary:

Because of their potentially fatal risk, particularly the presence of cardiac comorbities necessitates accurate internal and cardiac assessment and therapy prior to the initiation of any lymphological treatment. Lymphoedema, especially of the legs, may be overlapped by concurrent hypoproteinaemic or dysproteinaemic oedema (for instance in the presence of renal or hepatic diseases), by venous stasis of different causes (thrombosis, chronic venous insufficiency or postthrombotic syndrome), by peripheral vascular disease or by orthostasis in the case of immobility (61, 68, 71, 76). These conditions may impede the diagnosis of lymphoedema.

For medical expert reports, additional diagnostic imaging is recommended, even in the case of clinically unambiguous diagnoses. The same applies if invasive therapy is considered. The possibilities of quantifying advanced diagnostic imaging is described in chapter 3 (working group 3) of the guideline.

Working group 3: Advanced diagnostics

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1. What do advanced diagnostics consist of?

Advanced diagnostics comprise functional diagnostics, morphological imaging techniques, specific laboratory diagnostics as well as genetic diagnostics.

Consent 100% (strong consent)

2. When should basic diagnostics be supplemented with advanced diagnostics?

If no decisive result can be obtained by means of basic diagnostics, diagnosis should be made with advanced diagnostic procedures. Advanced diagnostics are used to verify the diagnosis of oedema, to establish or exclude morphological or functional disorders of the lymphatic drainage system as the cause of oedema, to plan surgical interventions and to monitor therapies.

Consent 96.9% (strong consent)

Commentary:

As a rule, the diagnosis of clinically manifested lymphoedema is easy and clinically reliable (see chapter Basic diagnostics). Advanced diagnostics are indicated in the case of restrictions and limitations of clinical diagnostics, differential-diagnostic and prognostic questions, in connection with surgical interventions on the lymphatic drainage system and when assessing conservative treatment measures.

1. What conditions may present an indication for advanced diagnostics?

1. Suspected subclinical lymphoedema (stage 0 / stage of latency) and lymphoedema stage I (primary and secondary lymphoedema),
2. Differentiating multifactorial oedema or oedema without any typical symptoms of lymphoedema or findings,
3. Planning surgical interventions,
4. Monitoring therapy and the course of disease,
5. Suspected thoracic or abdominal involvement, and

6. Preparing medical expert reports.

Consent 93.8% (consent)

Commentary:

Diagnostic imaging techniques are used to differentiate lymphoedema from oedema of multifactorial aetiology or in the case of oedema lacking the morphological changes typical for lymphoedema. Such imaging techniques may also be used when planning lymphatic surgery or surgical interventions carrying the risk of lasting detrimental effects on the lymphatic drainage system respective on the transport of lymphatic fluid.

When using imaging techniques, morphological diagnostics need to be differentiated from functional diagnostics. Morphological examination methods consist of sonography, magnetic resonance imaging and indirect lymphangiography. Functional diagnostic methods include the lymphoscintigraphic function test and fluorescence microlymphography. Experimental methods comprise bioelectrical impedance measurement and indocyanine green fluorescence lymphography. The latter method is used off-label for diagnosing oedematous diseases (country-specific).

Functional lymphoscintigraphy and fluorescence microlymphography are suitable methods for objectifying impaired lymph transport in patients who do not show any clinical changes. If clinical changes are present, the use of the listed imaging techniques depends on the invasivity, contraindications and side effects of the respective method. The decision which imaging technique is to be used depends on the individual situation.

4. What questions <u>cannot</u> be answered with advanced diagnostics?

Malfunctions of the lymphatic drainage system as the potential cause of oedema of the head, neck or trunk, malfunction in the extremities of paretic patients or inability of patients to sufficiently cooperate.

Consent 96.9% (strong consent)

Commentary:

In contrast to the evaluation of leakages, cysts, fistulae and lymphoceles, no specific examination device is available for assessing the function of lymph transport in the area of the head, neck and trunk. The same applies to the assessment of oedema of the legs in patients who are unable to fulfil the physical requirements necessary for functional lymphoscintigraphy.

5. How may the diagnosis of lymphoedema be confirmed in dependence on the method and stage?

Diagnosis of lymphoedema may be confirmed in dependence of the stage by means of the following methods:

	Stage 0/ stage of latency	Stage I	Stage II	Stage III
Basic diagnostics		(+)	+	+
Ultrasound scan			+	+
Lymphoscintigraphic function test	+	+	+	+
Indirect lymphangiography	(+)	(+)	+	+.
Fluorescence microlymphography	+	+	+	+
Indocyanine green lymphography*	?	+	+	+
Direct lymphography	c	c	c	c
Computed tomography			+	+
Magnetic resonance tomography			+	+

Consent 81.3% (consent)

Commentary:

c: Contraindicated to the diagnosis of lymphoedema but not to the diagnosis of malformations of the lymphatic drainage system and in the context of interventional and surgical measures.

+: Diagnosis of lymphoedema and disruption of the lymph transport can be confirmed with this method.

* off-label use.

Special conditions apply for babies and infants:

Babies and infants with the clinical diagnosis of lymphoedema may also be affected by malformation / angiodysplasia. For this reason, basic laboratory tests in addition to clinical diagnostics should be carried out routinely. Depending on the individual finding, targeted examinations with the appropriate device should be conducted at an early stage.

6. Methods of advanced diagnostics

Lymphoscintigraphic function test

The lymphoscintigraphic function test is used to quantify the transport of lymphatic fluid in the extremities. This method is based on quantifying the uptake of a radioactively labelled tracer in the regional lymph nodes – which is injected in the periphery and exclusively transported by the lymphatic drainage system – and on the determination of the transport time. The lymphoscintigraphic function test consists of two components: dynamic assessment and static lymphoscintigraphy. Dynamic assessment requires a specific physical load applied to the extremities to activate the transport of lymphatic fluid and thus depends on the capability of the individual patient to cooperate.

Indication:

- Assessment of the function of the peripheral lymphatic drainage system and objectification of lymphoedema primarily in primary and secondary lymphoedema stage 0 and stage I,
- In the case of swelling in the arms or legs of unknown aetiology,
- When planning and monitoring therapy in the case of microsurgical lymphatic interventions, and
- In plastic surgery of patients with lymphoedema (77-81).

Evaluating transport function of the lymphatic drainage system in the head, neck and trunk is not possible.

Contraindications and side effects:

No allergic reactions to the tracer have been described so far. This examination is contraindicated in pregnant women.

Further information:

Tracer and injection technique:

The examination is generally carried out as a comparison between the two arms or the two legs. Tc-99m-labelled nanocolloids are used as tracers, in Germany primarily Tc-99m-labelled nanocolloid human serum albumin. One single injection is subcutaneously injected into the distal back of the foot between the metatarsal heads of the first and second toe rays or in the distal back of the hand between the second and third finger rays. The amount of the injected radioactive dose depends on the specifications of the regulatory authorities (country-specific guidelines).

Dynamic assessment:

Physical load: Because lymphatic flow is too slow to be quantitatively assessed under resting conditions, the pumping function of the lymphangions is activated using standardised physical loads (78, 82-85). The optimal method for examining the legs during dynamic assessment is walking on the treadmill for a set amount of time and at a specific walking speed and cadence (86, 87). Alternatively, physical load may be induced by metronome- and

pedometer-controlled walking (88). Other methods of inducing physical load are less reliable. Arms are examined in supine position, and physical load is induced by rhythmic metronome-controlled fist closure.

Transport time:
Transport time is the difference between the beginning of inducing physical load and the first radioactive evidence in the regional lymph nodes.

Attenuation correction:
Calculating tracer uptake in lymph nodes not only requires correction for radioactive decay but also correction for attenuation (78, 82, 82-85). Radiation originating from radioactively marked lymph nodes is attenuated by the overlying soft tissue. Such attenuation grows exponentially with the depth of the lymph nodes. The depth of inguinal lymph nodes is up to one half-value layer (45 mm), whereas the depth of iliac and axillary lymph nodes is up to three half-value layers (135 mm). Thus, in the worst case, only one-eighth of the stored radiation may be measured (78). Calculation of attenuation correction generally requires knowledge of the depth of the lymph nodes. Single photon emission computed tomography (SPECT) represents an accurate but relatively time-consuming tomographic technology for determining the depth of lymph nodes, whereas the accuracy of ultrasound scanners is insufficient for this purpose (78, 89). Attenuation correction using the BMI-correction formula is a simple and accurate method for determining quantitative lymph node uptake by means of the lymphoscintigraphic function test of the legs (90). No BMI-correction formula is available for the upper extremities.

For the legs, the pathological range of lymph node uptake after a standardised 30-minute walk is below 7.48%, the grey area ranges between 7.48% and 8.39%, and the normal range is higher than 8.39%. For the arms, the normal range and the range of lymphoedema slightly overlap; after a 60-minute exercise, the normal range of lymph node uptake lies between 5.1% and 17.4%, whereas the uptake of lymphoedema is less than 5.3% (91). Tracers of different manufacturers may not be interchanged because of their different chemical and physical properties (92).

Interpretation of the findings:
The level of lymph node uptake depends on patient-related factors and the method of examination. Disorder of the lymph transport decreases lymph node uptake, and the same applies to insufficient activation of the pumping function of lymphangions due to inadequate physical exercise. Increased lymphatic load also increases lymph node uptake, for instance in young women with lipoedema (93) and in the early stages of chronic venous insufficiency. Uptake values in the normal range indicate unrestricted lymph transport, but such values are also found in patients with combined insufficiency of lymphatic drainage system. The ratio between lymphatic load and the extent of restriction in the transport capacity determines if the uptake is increased, seemingly normal or decreased (91, 93). Normal transport times do

not exclude any disorder of the lymph transport, but – in the case of using an accurate injection technique – decreased transport times are evidence of lymphoedema.

Static lymphoscintigraphy

Static lymphoscintigraphy is generally conducted as ventral whole-body scintigraphy or as partial body scintigraphy and, depending on the research question, as SPECT. Lymph collectors present as band-like accumulations of radioactivity. Storage of the radiopharmaceutical in lymph nodes leads to different focal radioactivity concentrations. This method is neither meant for differentiating the amount of lymph vessels and their lumen nor for assessing the size and structure of lymph nodes. Depending on the extent of transport disorder, lymph collectors and lymph nodes of the areas affected by lymphoedema are weaker and smaller, sometimes less clear or no longer definable. Pathological and localised radioactivity concentrations may reflect local damage to the lymph vascular system or to lymphoceles or lymphatic cysts. Areal distribution of the accumulation of radioactivity represents dermal back flow due to disrupted drainage and valve insufficiency. Complementary SPECT is more suitable than planar scintigraphy for assessing the proportion of dermal back flow (94, 95).

Indocyanine green fluorescence lymphography

Indocyanine green (ICG) is an established tool for assessing hepatic and cardiac function as well as a method of retinal angiography. The first examinations of lymph vessels were used for monitoring lymphovenous anastomoses (96, 97). Over the years, most published studies concentrated on patients with secondary and hence predominantly descending lymphoedema, which also explains the proposal of a classification system for fluorescence lymphography from proximal to distal (98, 99). A classification system for primary lymphoedema has also been proposed (100).

Indication:

At the time of printing, ICG is used off-label for the indication of lymphoedema. Indocyanine green fluorescence lymphography is being assessed for therapeutic monitoring after surgery, during lymph drainage and for diagnosing lymphoedema. No standard has yet been established for diagnosing lymphoedema. The maximum viewable distance is about 2 cm.

Contraindications and side effects:

Contraindications: Erysipelas at the site of injection.

Side effects: None known for fluorescence lymphography. After intravenous injection, patients with and without any known hypersensitivity to iodine have shown anaphylactic and urticarial reactions. For further side effects in the case of intravenous injection, see the drug information provided by the manufacturer.

Further information:

After subcutaneous injection, ICG binds to albumin, which in turn is drained via the lymphatic drainage system. Literature reports have not only described qualitative criteria, such as the pattern of distribution (dermal back flow, obstructed fluorescence images with dilatation and tortuosity, Milky Way sign, less enhancement and no enhancement [100, 101] as well as linear, splash, stardust and diffuse [98, 99]) but also transit times until drainage in the inguinal area (102). In healthy people, these transit times correlate with those of dynamic lymphoscintigraphy (102). Studies on secondary lymphoedema of the arms have also yielded a pattern of distribution which is different to that of healthy people (103). Lymph pumping pressure is measurable with indocyanine green fluorescence lymphography (104).

The maximum levels of absorption and emission of indocyanine green are close to the infrared spectrum: for fluorescence measurements, maximum absorption is at about 800 nm and maximum emission at about 830 nm. Tissue may be penetrated by this kind of fluorescence.

Methods:

According to the references, 0.1-0.3 ml (98, 99, 101, 102) of indocyanine green 0.25-0.5% (98, 99, 102) is subcutaneously injected into the back of the foot or the back of the hand with a 27-gauge needle. After the injection into the back of the foot, the patient stands up. The route of lymphatic drainage is observed with an infrared camera under excitatory illumination and documented with photos and videos. The infrared camera has an excitatory light source (LED) with a wavelength of 760 nm, which filters out light with wavelengths below 820 nm.

Sonography

Indication:

In the diagnostics of lymphoedema, sonography is primarily used to obtain evidence of interstitial fluid and secondary tissue alterations (particularly increase in fatty tissue as well as fibrosis and fibrosclerosis), to differentiate localised swelling, in the diagnostics of lymph nodes and to establish the cause of secondary lymphoedema. Sonography is a suitable method for monitoring the treatment and follow-up care of lymphoedema but unsuitable to prove lymphoedema. In contrast, sonography plays a key role in establishing the diagnosis of phleboedema and phlebolymphpoedma and the causes of secondary lymphoedema.

Interstitial fluid and oedema:

The quality of the ultrasound scanner and the software used determines whether ultrasound images of oedema or any other interstitial fluid accumulation show liquid structures and/or echogenic and/or finely dispersed structures next to anatomical factors, namely the width of the liquid structures (105-107). No correlation could be found between the nature and extent of ultrasound images of oedema and the severity of disrupted lymph transport (106).

Summary:
In most patients, early-stage lymphoedema cannot be diagnosed by means of sonography. In the diagnostics of lymphoedema, sonography is mainly used to prove the presence of interstitial fluid and secondary tissue alterations, to differentiate localised swelling, in the diagnostics of lymph nodes and to establish the cause of secondary lymphoedema. Sonography in combination with mammography may also yield important information on mammary oedema, particularly after breast-conserving therapy for breast carcinoma. In general, sonography (or any other imaging technique) is required for the diagnostics of lymphoedema stage II and III. Sonography is useful for monitoring the therapy and follow-up care of lymphoedema and is indispensable for establishing the causes of phleboedema and phlebolymphoedema.

Further information:
Oedema due to lymphoedema cannot be differentiated from epifascial interstitial fluid accumulation by means of sonography in the case of bleeding, phlegmonous inflammation, cardiac oedema or any other interstitial fluid accumulation with a three-dimensional reticular distribution pattern. The often wider dissemination of visible fluid in the deeper subcutis is also non-specific. The previously used term ’lymphatic clefts’ is incorrect because the fluid is localised in the interstitium (prelymphatic channels), which is not part of the lymphatic drainage system. By definition, interstitial fluid is not to be equated with lymphatic fluid, except in the case of extravasates from a lymphatic vessel.

Lymph vessels:
Because initial lymph vessels (lymph sinus) measure between 10 and 100 µm in diameter and lymphatic collectors between 100 and 600 µm, they are partly below the resolution of the ultrasound frequency of 14 MHz (108, 109). Lymphoedema show various alterations both in initial lymph vessels as well as in lymph collectors. These alterations range from hypoplasia to hyperplasia and dysplasia and include varicose changes such as dilatation, broken vessels and changes in diameter. Therefore, ultrasound visualisation of initial lymph vessels is not possible, whereas lymph collectors can be partly depicted, at least in theory. In reality, depending on the equipment, non-dilated epifascial collectors of the legs are often not detectable or at least difficult to differentiate from nerves and veins, even when using amplitude-coordinated flow representation or duplex sonography. A missing flow signal in the tubular structure of the extremities is not a sufficient criterion for differentiation from veins and lymph vessels.

Ultrasound scans enable visualisation of dilated lymph vessels with a diameter of more than 3 mm, for instance in the case of primary lymphoedema with hyperplasia, in secondary lymphoedema with congestion of the lymph vessels and particularly in filariasis. Occasionally, visualisation of filaria is possible in the case of filarial infection of lymph nodes (filaria dance sign) (110). In adolescents and adults, the main junction of the thoracic duct can nearly always be visualised. Amplitude-coordinated flow representation and duplex

sonography are important devices for functional assessment because they facilitate anatomical orientation (111).

Fibrosis and fibrosclerosis:
Tissue compressibility can be semi-quantitatively assessed and documented by means of sonography. Limited compressibility may indicate fibrosis or fibrosclerosis; however, compressibility may also be limited in firm oedema.

Lymph nodes:
Lymph node atrophy and hypoplasia in the groin are easy to visualise. Assessment is based on qualitative criteria, the size of the lymph nodes and the amount of lymphatic tissue (cortex, paracortex and medulla) presenting as hypoechoic rim (112). Axillary lymph nodes often show pronounced involution already in middle age, so that differentiation from lymphoedema-associated atrophy seems to be problematic.

Chylous reflux:
An important field of application of sonography is providing evidence of even small amounts of intra-thoracic, intra-abdominal as well as pericardial fluid in syndromes associated with impaired lymph transport and chylous reflux. Sonography is also used in the diagnostics of lymphoceles, which cannot always be sonographically differentiated from seroma without conducting any additional scintigraphic or dye tests. For diagnosing lymphangioma, magnetic resonance tomography (MRT) is preferable to sonography because MRT enables more accurate assessment of extension and boundaries.

Further questions:
The differentiation, localisation and quantitative assessment of erysipelas from fasciitis, abscess formation and phlegmons by means of sonography is generally easy; here, all sonographic criteria for oedema can be observed.

Practical recommendations:
For clinical practice, the following conclusions may be drawn: Anechoic or unechoing ‘clefts’ – even those presenting with a ‘hyperechoic rim’ (depending on the quality of the ultrasound scan and its settings) – are not findings typical for lymphoedema; such ‘clefts’ are just evidence of the presence of interstitial fluid (113). In lymphoedema, fluid formation may only be detectable from stage I onwards. If the ultrasound scan does not show any thickening of the dermis or subcutis, diagnosis of lymphoedema cannot be excluded. If clinically indicated, thickening of the cutis is a typical symptom of lymphoedema stage II and III. Finely dispersed structures and increased echogenicity are not criteria specific for fibrosis because they are present in almost all oedema of different aetiologies and should thus be targeted in the diagnostics of oedema (105, 106). Limited sonographic compressibility and widened hyperechoic areas in the subcutis and the fasciae may be an indication for fibrosis.

Indirect lymphography

Indirect lymphography represents a radiological examination method which allows the morphological visualisation of peripheral lymph vessels at selected body sites.

Indication:

Indirect lymphography is used to obtain information on morphological changes of superficial lymph vessels for overall disease assessment. Such questions may arise when assessing swelling of the limbs of unknown aetiology, particularly if the lymphoscintigraphic function test is not possible, in the case of localised or generalised soft tissue swelling of the extremities or the trunk due to primary or secondary lymphoedema or combinations such as lipolymphoedema or phlebolymphoedema (114-120).

Contraindications: Known intolerance to contrast agents and erysipelas at the site of injection.

Further information:

Methods:

A water-soluble, non-ionic X-ray contrast agent is injected strictly subepidermally, either by means of an infusion pump or manually. A localised deposit of the contrast agent is formed at the site of the injection, from which the contrast agent is transferred to the lymph vessels. Indirect lymphography enables the visualisation of precollectors and collectors measuring between 20 and 40 cm in length. In the case of hypoplasia of the collectors, precollectors and dermal initial lymph vessels are widened (dermal back flow). Central lymph vessels and lymph nodes can generally not be depicted. Examination-dependent variables are the site of injection (region of interest), the rate of infusion (0.12 to 4 ml/min), the catheter, the contrast agent (Isovist 300 approved for ILG) and the duration of the examination (5 to 30 min).

Side effects:

Erythema at the site of injection, burning sensation during the infusion and skin necrosis.

Direct lymphography

Direct lymphography is a radiological examination method for visualising lymph vessels and lymph nodes.

Indication:

Direct lymphography is used in the interventional therapy of the lymphatic drainage system (121-124). Moreover, direct lymphography is also used in the case of refractory lymphatic fistulae in the inguinal, retroperitoneal and thoracic regions because the discharge of the contrast agent via the fistula facilitates the development of granulation tissue and thus the closure of the fistula. Direct lymphography has the highest reporting value when assessing morphological changes in the lymphatic drainage system. However, the application of this

method in routine diagnostics has been discontinued because of its high methodological complexity and particularly because of its considerable side effects.

Contraindications:
Direct lymphography is contraindicated in the diagnostics of lymphoedema because of the high risk of disease deterioration (125). Allergy to patent blue and sensitivity to the contrast agent.

Further information:
Methods:
A lymph collector at the back of the foot or hand, which has been dyed with patent blue, is surgically exposed. An oil-based contrast agent is directly injected into the lymphatic vessel by means of an infusion pump. Images are documented directly after administration of the contrast agent (lymphangiographic phase) as well as after 24 und 48 hours (lymphadenographic phase). Lymph vessels and lymph nodes of the trunk are depicted by means of intranodal lymphography. Here, the contrast agent is injected into a lymph node under sonographic control.

Side effects:
Deterioration of lymphoedema, pneumonia and fat embolism.

Magnetic resonance tomography
Lymphoedema:
Magnetic resonance imaging (MRI) enables sensitive and specific diagnostics of oedematous changes in the soft tissue including the skin. MRI can visualise regular lymph collectors, narrow-lumened or dilated lymph vessels, areas with increased fluid retention and damages to the regional lymph nodes. MRI may be carried out with or without a contrast agent (126). Moreover, lymphatic flow cannot be measured by means of invasive methods (127). In contrast to the lymphoscintigraphic function test, subclinical lymphoedema cannot be diagnosed by means of MRI.

Lymphatic malformation:
MRI is the gold standard for diagnosing lymphatic malformations, which represent the second most common vascular malformations. On MR images, lymphatic malformations present with lobules and septae. Signalling ranges from intermediary to attenuated in T1-weighted images but is increased in T2-weightes images. Without the intravenous injection of a contrast agent, lymphatic malformation is difficult to differentiate from venous malformation (128). Lymphatic malformations generally do not show any contrast agent uptake.

Contraindications and side effects:
Contraindications to MRI are presence of metallic foreign objects and implants, for instance cochlear implants or pace makers, as well as contraindications to the contrast agent in the case of renal dysfunction or allergies.

Further information:
In the past, systemic imaging of the lymphatic drainage system by means of MRI was limited to the morphological visualisation of lymph nodes. The size of lymph nodes (>2.5 cm in the inguinal region) was of particular importance in this context. Pathological lymph nodes have a spherical shape and typically lack the fatty hilum. Nevertheless, even lymph nodes with a normal appearance and a fatty hilum may be affected by micrometastases. In such cases, diagnostic accuracy may be increased with other diagnostic methods, for instance dynamic contrast-enhanced MRI and diffusion-weighted MRI; however, a considerable number of lymph nodes affected by metastasis are not detected by these imaging methods. Dynamic contrast-enhanced MRI is a well-established clinical method, in which a series of images is taken during the intravenous injection of a gadolinium-containing contrast agent. In the subsequent image analysis, ‘wash-in’ and ‘wash-out’ curves are generated. This technology is useful for identifying pathological lymph nodes (129). Sensitivity is 100%, specificity 56% and NPV 100%.

Nowadays, MRI also enables the visualisation of lymph vessels in lymphoedema to assess the morphology, lymphatic flow, draining lymph nodes (for instance sentinel lymph nodes) and surrounding anatomical structures and therefore also the underlying aetiology. The demands on MR technology correspond to those on periphery MR angiography. MRI scanners with a magnetic field strength of 1.5T or 3T are widely available by now, whereas the technology of MR lymphangiography is relatively new and thus only established at a few centres.

Lymphoedema:
Visualisation of lymphoedema without the administration of a contrast agent is already possible by using high-resolution T2-weighted sequences (130). Magnetic resonance lymphography (MRL) is a promising three-dimensional method (131), which requires a contrast agent; however, this technology has only been established at very few centres so far. The technological requirements of MRL correspond to those of periphery MR lymphangiography. MRL is minimally invasive and has a significantly lower complication rate than conventional lymphangiography.

Several gadolinium-containing contrast agents are available. Paravasal administration is used off-label; however, extravasation due to gadolinium-containing contrast agents is rather common and mostly unproblematic in clinical routine.

So far, gadolinium-containing contrast agents for MRL have not been systematically compared. As a relatively new method, MRL is very suitable for assessing the anatomy of

lymph vessels and their drainage in extremities affected by lymphoedema (132). For this purpose, a gadolinium-containing contrast agent is intracutaneously injected between the toes. 3D-sequences are acquired at staggered intervals. Spatial resolution is about 1 mm, and temporal resolution for the entire lower extremity is about 10 minutes. Dynamic approaches have also been described in several studies, from which anatomical as well as functional information can be derived. Extremities affected by lymphoedema show differences in the number of lymphatic vessels as well as in vessel diameter (between 0.5 and 8 mm). Uptake of the contrast agent is increased in both lymph vessels and lymph nodes. Lymphatic flow may be observed in real time in MRL in contrast to lymphangiography and lymphoscintigraphy. This technology is also useful for the morphological visualisation and classification of primary lymphoedema. Intact lymph vessels are thin and have a string-of-pearl appearance. Primary lymphoedema is marked by diffuse lymphatic drainage and particularly by rarefaction and dilatation of the remaining lymph vessels. MRL also enables visualisation of damaged lymph vessels as the cause of dermal back flow in secondary lymphoedema (133). Next to lymph vessels, changes in the surrounding structures, such as soft tissue oedema, fibrosis or tumours as possible causes of lymphoedema, may also be depicted by means of MRL (134). Moreover, MRI is also highly suitable for the anatomical visualisation of the lymphatic status prior to surgical intervention and for monitoring postoperative care. Overall, there are only very few clinical studies involving lymphoscintigraphic correlation. In this context, MRL shows high diagnostic accuracy of >90%, particularly with regard to providing evidence on pathological changes in lymph vessels. For depicting diffuse lymphatic drainage, however, MRL is slightly less suitable than lymphoscintigraphy. At present, MRL should be mainly used as a complementary tool to scintigraphy and in preoperative diagnostics. Only a few case reports but no systematic clinical studies are available for the trunk and the upper extremities.

Fluorescence microlymphography

Fluorescence microlymphography is a practice-based examination enabling the diagnosis of lymphoedema particularly in the case of clinically obscure oedema (136). The pivotal criterion for the diagnosis of lymphoedema is the radius of fluorescein isothiocyanate-dextran (FITC dextran) diffusing in the superficial lymph sinus (synonym lymph capillaries) after a small intracutaneous depot injection. In primary and secondary lymphoedema of the legs, a radius with a cut-off of ≥12 mm has the highest sensitivity and a radius with a cut-off of ≥14 mm the highest specificity (136, 137). A further indication for lymphoedema is cutaneous reflux; however, no solid statistical data are yet available in this context. Lymph sinuses are absent in rare aplastic and hypoplastic lymphoedema (138, 139). Occasionally, lymph precollectors are found. Deep lymph vessels cannot be visualised by means of microlymphography. Studies have shown a significant difference in the diffusion of dye between patients with secondary lymphoedema of the arms and healthy people (140, 141). Fluorescence microlymphography is available in Switzerland but not in Germany or Austria.

Indication:
Fluorescence microlymphography is used for diagnosing lymphoedema in the case of clinically obscure oedema, oedema of mixed aetiology and lymphoedema stage 0.

Contraindications and side effects
Contraindications:
Erysipelas at the site of injection.
Rare side effects:
(0.5-1.1%) temporary itchiness and eczematous skin changes at the site of injection (136, 137).

Further information:
Microlymphography with FITC dextran is based on the fact that interstitial macromolecules with a molecular weight of more than 20'000 Da are primarily drained via lymph sinuses (142). FITC is excited by light with a wavelength of about 495 nm and emits light with a wavelength of about 521 nm. Lymph sinuses filled with FITC dextran may be visualised with commercially available reflected-light microscopes for fluorescence microlymphography with FITC filters or by means of light sources with suitable wavelengths. The reason why FITC dextran expands into dermal sinus tracts in lymphoedema is not yet known. It may be possible that the dermal lymphatic network acts as a collateral circulatory system with low resistance to deep subepidermal lymph collectors (the normal manner of drainage), which show high resistance due to obstruction or inadequate pumping function.

Methods:
0.1 ml of a 25% solution with FITC dextran (Fluorescein isothiocyanate-marked dextran with a molecular weight of 150'000 Da) is bilaterally and strictly intracutaneously injected as a depot or as a wheal with a tuberculin syringe and a 25-gauge needle. 10 minutes after the injection, the maximum diffusion of FITC dextran in lymph sinuses is observed over an FITC emission filter with about 495 nm exposure. Diffusion of FITC dextran ─ measured radially from the rim of the depot and compared to the opposite side ─ is documented by means of photos and videos.

Sensitivity and specificity as evidence of lymphoedema (60):
12 mm cut-off: 0.94/0.79
14 mm cut-off: 0.91/0.86

Device:
Light sources or white light plus filter with a wavelength to excite FITC (495 nm), filters with an FITC-emitting spectrum (521nm) for observation and documentation.

Standardisation:
0.1 ml of Fluorescein isothiocyanate dextran with a molecular weight of 150'000 Da in a 25% solution with sodium chloride 0.9%.

Specific laboratory tests

Indication:

No specific laboratory tests are available for diagnosing lymphoedema. In the case of suspicion or any indication of comorbidities that may exacerbate lymphoedema, laboratory tests should be conducted, for instance for assessing cardiac function. Laboratory tests may also become necessary in the case of suspected involvement of the lymphatic drainage system in the thorax or abdomen and/or suspected lymph reflux diseases (143, 144).

Further indications for laboratory tests:

Analysis of puncture specimens of (chylous) effusions (chylopericardium, chylothorax, chyloperitoneum, chylarthrosis and lymphostatic enteropathy) to differentiate transudate, exsudate and chylous effusion.

Genetic diagnostics

With regard to genetic diagnostics, see chapter working group 1 ‘Definition and Epidemiology, section 5: Molecular basics of primary lymphoedema’.

Diagnosing capillary permeability

Increased capillary permeability can be diagnosed by means of the water load test (modified Streeten test).

Indication:

Fluid retention syndrome and idiopathic oedema.

Methods:

Measurement of the weight and volume of the legs prior to the examination, emptying of the bladder, drinking 20 ml of still water per kilogramme of body weight within 30 minutes. Orthostasis for 4 hours during which urine is collected (including emptying of the bladder at the end of the examination). Once again measurement of the weight and volume of the legs.

Pathological findings are confirmed if urinary excretion within these 4 hours is less than 60% of the liquid intake and if the volume of each leg has increased by more than 250 ml. Pre-requisite of the examination is the prior exclusion of general cardiac, renal, hepatic or drug-induced oedema and relevant chronic venous insufficiency. If medically appropriate, diuretic therapy has to be discontinued on time. On the test day, patients should refrain from smoking before the examination (145, 146).

Working group 4: Conservative therapy

Etelka Földi, Ute-Susann Albert, Susanne Helmbrecht, Malte Ludwig, Anya Miller, Michael Oberlin, Hans Ortmann, Christian Schuchhardt, Eva Streicher, Gerson Strubel, Stephan Wagner and Christian Wiederer

Introduction

Lymphoedema constitutes a chronic disease that requires treatment. Lymphoedema may develop at any age. Primary lymphoedema is more common in childhood, whereas secondary lymphoedema more often develops with increasing age. Adequate therapy including both conservative and surgical treatment may prevent disease progression. If therapy is started at an advanced stage, the treatment aim is complete regression or at least regression to a lower stage.

1. What does conservative therapy of lymphoedema consist of?

Standard therapy of lymphoedema is Complex Decongestive Therapy (CDT), which consists of the following coordinated components:

- Skin care and, if required, treatment of skin diseases/skin lesions,
- Manual lymphatic drainage, complemented if required by additional manual techniques,
- Compression therapy with specific multi-layer compression bandage systems and/or lymphological compression stockings,
- Decongestive sports and exercise therapy, and
- Information and instruction on self-treatment.

Consent 100% (strong consent)

Commentary:

Complex Decongestive Therapy (CDT)

CDT therapy consists of two phases: Phase I is aimed at mobilising the increased interstitial fluid to normalise tissue homeostasis. The aim of phase II is maintenance and optimisation of the therapeutic success (68, 147-152). Indications, contraindications and the application of individual therapeutic measures depend on several factors: the stage of lymphoedema at the start of treatment, comorbidities, the age of the patient and the patient's individual life circumstances. In phase I of the treatment, all components of CDT are used once or twice a day. Patients are treated in specialised centres with appropriate infrastructures, either in an in-patient or an out-patient setting (153).

In phase II, the components of CDT are applied according to the individual oedema findings. Depending on the course of disease, phase I may have to be repeated, particularly in the case of intercurrent diseases (154, 155).

2. What are the aims of conservative therapy of lymphoedema?

Conservative therapy is aimed at reducing disease symptoms to the symptom-free stage or at least at lowering the stage of disease to achieve long-lasting stability of disease, to improve quality of life, to enable participation in social and professional life and to prevent complications. The combination of CDT with both self-management and information ensures long-lasting therapeutic success.

Consent 100% (strong consent)

Commentary:

To define therapeutic targets, the clinical findings should already be accurately documented at the start of conservative therapy of lymphoedema (diagnosis and course of disease documentation, Ortmann/Streicher [156, 157]). Concomitant diseases aggravating lymphoedema may increase therapeutic requirements. Furthermore, the course of disease should be documented (156). Long-lasting therapeutic success depends on the effectiveness of the treatment chain consisting of physician, physiotherapists/massage therapist/lymph therapist, health care supplier and the affected patient (158).

Therapeutic targets in childhood: Conservative therapy in childhood needs to be suitably adapted to the respective age and involves direct participation of the parents. This setting enables school education and vocational training and reduces the psychological burden of the disease. A study has shown a significantly higher reduction in oedema and better disease stability in children treated by both well-instructed parents and physiotherapists than in children treated by physiotherapists only (159, 160).

Therapeutic targets in adults are preservation of work and earning capacity and, particularly in elderly people, prevention of care dependency (21, 161).

3. What is the mode of action of Complex Decongestive Therapy (CDT)?

- Mobilising and reducing pathologically increased interstitial fluid including drainage of lymphatic waste products,
- Improving disturbed homeostasis in the interstitium and reducing statis-induced inflammatory processes, and
- Reducing altered connective tissue.

Consent 100% (strong consent)

Commentary:

In daily practice, the following clinical symptoms are considered benefits of CDT: Significantly reduced swelling of the affected body site, decrease in stasis-related problems such as heavy legs and feeling of tightness of the skin, increase in mobility and regeneration or

significant improvement of lymphostatic skin changes. Furthermore, sonographic ultrasound examinations have shown that correctly applied CDT in combination with compression bandages reduce lymphostatic fibrosis and fibrosclerosis (162, 163). As a long-term effect, episodes of erysipelas have been reduced (164-172).

The effects of the individual therapeutic components of CDT:

Manual techniques in the treatment of lymphoedema:

Lymphoedema should be treated with manual lymphatic drainage (MLD), consisting of four basic grips that produce a stretch stimulus on the cutis and subcutis. The pulsation rate of lymphangions is increased by stretching the lymphatic vessel walls, which increases the lymph flow in the collectors and consecutively facilitates the formation of lymph fluid (absorption of tissue fluid in initial lymph vessels), thus reducing the pathologically increased interstitial fluid content.

Additional manual techniques should be employed at stage II and III with the aim of softening tissue indurations. In the presence of orthopaedic or neurological concomitant diseases, further physiotherapeutic techniques should be integrated into CDT to reduce functional deficits (158, 166, 173-176).

Compression therapy

A further essential component of CDT is compression therapy with the following effects:

- Normalisation of the pathologically increased ultrafiltration with consecutive reduction of lymphatic waste products,
- Increased influx of interstitial fluid into initial lymph vessels,
- Movement of the fluid through the tissue channels,
- Increased lymph flow in the lymph vessels that are still working sufficiently,
- Reduction of venous pressure resulting in an antioedematous effect, and
- Improving the tissue status in phase II (162, 163, 177, 178).

In phase I, compressions should be applied in the form of lymphological multi-layer bandages (179-183).

In phase II, patients are supposed to wear flat-knitted tailor-made medical compression stockings (184), which have a similar elasticity as textile elastic short-stretch bandages. By medium use, such compression stockings ensure effective compression pressure for approximately six months. Some patients may require two sets of compression stockings worn on top of each other. A second pair of stockings is required for hygienic reasons. Patients undergoing intensive physical exertion or patients with a changed lymphoedema status may require new sets of medical compression stockings at shorter intervals.

Some patients may use a combination of compression stockings during the day and self-applied compression bandages during the night.

Multi-layer compression bandages should be used as follows:
Skin protection with a tubular bandage followed by a foam compression bandage and/or padding material. Additional material is required for finger and toe bandages. Compression pressure is adjusted by means of textile elastic bandages and may be supplemented with long-stretch bandages during the day in some patients. Joint flexibility must not be restricted. Pressure should be evenly distributed in order to avoid constriction. Therapeutic compression pressure is generally higher in the lower extremities than in the upper extremities.

Patients with lymphoedema stage II and III require compression therapy on a permanent basis.

The type of compression stocking required may change over the course of life, depending on:

- Changes in the lymphoedema, and
- Development of other concomitant diseases (for instance, orthopaedic, neurological or internal diseases).

Decongesting exercise and breathing therapy
Exercise therapy and sports activity are additional effective components of CDT. Muscle and joint pumps are activated by specific exercises: Contraction of the skeletal muscles increases interstitial pressure and thus the motor activity of the lymphatic drainage system. This effect is intensified by simultaneous external compression (185, 186).

Intensive breathing therapy increases both venous blood flow and lymph flow (185). Exercise and physical activity are part of phase I of CDT, which should be continued in phase II. A follow-up training programme according to the respective age and occupation should already be planned in phase I. Particularly suitable are group gymnastics for metabolic training, rehabilitation sports as well as the following types of sports:

- Walking – Nordic walking,
- Cycling – home trainer,
- Swimming and aqua aerobics (special attention should be paid to hygiene and the water temperature),
- Medical training therapy and moderate weight training (if necessary, in sport studios supervised by a physiotherapist), and
- Cross-country skiing.

Skin care and skin regeneration:
<u>Skin protection</u>
Compression materials put strain on the skin by reducing moisture and the lipid content of the skin. For this reason, skin protection and skin care are important therapeutic components, which should be carried out daily in order to avoid secondary infections, for

instance due to the development of fissures, and to maintain the barrier function of the skin (187). Suitable for cleansing the skin is pH-neutral soap, which needs to be rinsed off well. Glycerine is an important basic substance for maintaining moisture and the lipid content. Ceramides as physiological lipids and shea butter increase the fat content, facilitate the penetration of active substances and – in combination with urea – support the acid mantle of the skin. Humectants such as urea and glycerol maintain moisture and have a keratolytic effect. At higher concentrations, urea has also an antibacterial effect (188-191).

A key factor is the base of the skin product. Mostly dry skin is best treated with creams with a high fat content. Although skin lotions have a pleasant cooling effect and are quickly absorbed by the skin, they dry out the skin in the long run. Exemptions are lipolotions. Oily cream bases may be considered on cool days when less sweat is evaporating from the skin. The requirements of the different skin types should always be taken into consideration. Skin folds with a moist environment may require additional disinfection, for instance with polyvidone or octenidine (189, 191). Fast-absorbing hand creams may be used during the day and richer creams during the night.

The tolerability of the compression material in combination with skin care products depends on the ingredients of the care product and the composition of the compression material. Natural latex is sensitive to urea and paraffinum liquidum. Elastodiene, which is processed in most compression stockings, is not sensitive to urea up to 10% and mostly not sensitive to paraffinum liquidum (192). Therefore, skin care products may be applied shortly before wearing the compression stockings.

Skin regeneration

Skin injuries with subsequent superinfection result in the progression of oedema. For this reason, wounds should be disinfected as soon as possible, for instance with polyvidone or octenidine. The same applies to ruptured cysts and fistulae. Interdigital macerations due to fungal infection of the feet or hands as well as bacterial superinfections need to be treated according to the causative pathogen.

Eczematous skin changes, allergic reactions or insect bites may require temporary topical treatment with steroids. Skin diseases such psoriasis, neurodermitis or blistering dermatoses may aggravate oedema or are exacerbated by compression therapy. Affected patients require intensive topical and sometimes systemic treatment as well as suitable compression material. Potential allergies should also be taken into consideration (189, 190).

Information and instruction:

Patients often find CDT tiresome, particularly at the beginning of therapy, and always time-intensive. In addition, patients have to cope with the psychological burden of knowing that they will require treatment for the rest of their life because of the incurability of lymphoedema. Lack of treatment success often leads to helplessness, which reduces patients' adherence to therapy and facilitates further complications. The only way to counter such situations is to

inform the patient on how the lymphatic drainage system works, on the effects of the different therapeutic components of CDT and how they are built on one another and on the consequences of not adhering to therapy. The aim is that the acquired knowledge will improve self-management, thus improving quality of life and the course of disease. Pre-requisite for such improvement is the appropriate organisation of daily life (159).

Written information is useful, particularly at the beginning of therapy, followed by instructions during which also specific questions on the lymphatic drainage systems may be answered. Further topics of instructions should be skin care, breathing techniques, decongestion gymnastics and self-application of bandages. Cooperation with self-help organisations is recommended. Some patients may benefit from psychological counselling and others from the support of a self-help group in order to keep up courage and adhere to the therapy, particularly in the case of setbacks and disease deterioration.

4. What is the dosage of Complex Decongestive Therapy (CDT)?

The frequency and intensity of the components of CDT in phase I and phase II should depend on the clinical oedema findings and stage of the lymphoedema and be adapted to clinical changes.

Consent 100% (strong consent)

Commentary:

Because of the lack of available data in the literature, a strict differentiation between the stages of lymphoedema is difficult, both in a clinical as well as a pathomorphological context. From a clinical point of view, the different stages of lymphoedema are described as follows:

Stage 0 of lymphoedema / stage of latency / subclinical stage: Impaired capacity of lymph transport, no clinical evidence of oedema. Diagnosis of lymphoedema can only be established by means of apparative methods.

Stage I of lymphoedema: Swelling of the affected body site due to increased interstitial fluid. Upon palpation, the oedema is soft and pitting, depending on the position of the body, and of changing intensity. Phase I of CDT consists of the application of skin care, manual lymphatic drainage, lymphological multi-layer compression bandages and decongesting physiotherapy for up to 21 days. The dosage of the components of CDT in the subsequent phase II depends on the individual disease status, according to which CDT may be applied as intermittent or continuous treatment.

Stage II of lymphoedema: Presence of increased swelling progressively independent of the position of the body. Skin folds are enlarged, and the tissue consistency is increased. Lymphoedema stage II is associated with increased therapeutic requirements. During phase I of CDT, manual lymphatic drainage is applied twice a day in combination with multi-

layer compression bandages and decongesting exercises. Further measures are adequate skin care and instruction in self-treatment. Phase I mostly lasts 28 days.

Phase II of CDT is applied continuously: Manual lymphatic drainage is carried out on a regular basis depending on the individual disease status. Compression therapy with medical compression stockings is more complex and may consist of several layers of compression. In many patients, lymphological compression bandages are indicated, if appropriate as part of self-treatment. The same applies to decongesting exercises. Skin care must be more extensive to avoid the development of erysipelas. Because of the extensive therapeutic requirements involved, phase II of CDT represents a long-term therapy. The dosage of the individual components of CDT often needs to be adapted according to the respective disease status over many years. In the case of deteriorating oedema, phase I of CDT may have to be repeated.

Stage III of lymphoedema is marked by an excessive increase in altered connective tissue. The skin often shows lymphatic cysts and subcutaneous fistulae or red-livid coloration without overheating due to stasis dermatitis. Successful treatment in phase I is generally only possible on an in-patient basis. In the case of recurrent erysipelas, antibiotics can be administered as prophylaxis. Phase I may last up to 35 days. Because of the extensive therapeutic requirements involved, phase II of CDT represents a long-term therapy. The dosage of the components of CDT often needs to be adapted over many years according to the respective disease status at the time.

5. May the single components of Complex Decongestive Therapy (CDT) be applied in isolation?

Isolated application of single components is not recommended; Complex Decongestive Therapy (CDT) should be used in its entirety.

Consent 100% (strong consent)

Commentary:

Many publications have shown that CDT yields significantly better therapeutic results than the isolated application of its single components (153, 175, 176, 193-195). CDT represents a coordinated therapeutic concept for the treatment of lymphoedema. Many literature reports have shown that manual lymphatic drainage (MLD) alone is insufficient to treat lymphoedema and to prevent complications of lymphoedema. Full-body treatment may reduce the volume of lymphoedema to a certain extent when measured immediately after the treatment; without compression, however, the oedema will increase again within a few hours (195, 196). In patients with lymphoedema, particularly in those with lymphoedema also affecting the quadrants of the trunk, isolated compression therapy of the extremities may increase swelling at the root of the extremity and may even lead to genital lymphoedema (197). MLD in combination with compression therapy without skin care and, if necessary,

skin regeneration, may lead to skin damage and even erysipelas. The effectiveness of CDT with manual lymphatic drainage, compression therapy and skin care may be increased by exercising and leading an active lifestyle.

6. What diseases or conditions require modification of Complex Decongestive Therapy (CDT) for lymphoedema?

The following aspects should be considered in a modified version of CDT:

- Age,
- Concomitant diseases,
- Multimorbidity,
- Malignant lymphoedema / palliative care situation, and
- Posttraumatic or postoperative oedema.

Consent 100% (strong consent)

Commentary:

Modified conservative treatment of lymphoedema is understood as the modified and individually adapted application of the individual components of CDT. Manual lymphatic drainage or manual techniques: Certain parts of the body need to be excluded from treatment in order to avoid side effects. Compression therapy: The intensity of lymphological compression bandages needs to be varied with regard to pressure and the padding material. The condition of the skin and the mobility of the patient also have to be taken into consideration (risk of falling!).

Decongesting exercises and sports therapy: With regard to exercising, the decisive criterion is the physical fitness of the patient (198).

• Age:

Conservative therapy should be modified according to the age of the patient. In children, compression therapy should not be started before the age of 6 months. Compression pressure should be greatly reduced in order to avoid damage to the skin. The same applies to geriatric patients.

• Concomitant diseases:

In the case of lymphoedema of the extremities and the presence of concomitant diseases affecting lymphoedema, CDT should be supplemented with integrated medical and psychotherapeutic care including drug therapy, if necessary (199-206). Concomitant diseases may exacerbate lymphoedema in several ways: Diseases that increase the permeability of blood capillaries, for instance diabetic microangiopathy, increase the amount of lymphatic waste products in combination with restricted transport capacity. Limited mobility due to pain in the joints decreases the effectiveness of joint and muscle pumps.

• Multimorbidity:
In geriatric patients, lymphoedema frequently develops in combination with orthopaedic or neurological diseases, or both, which considerably reduces mobility. Such patients should be treated with physiotherapy to facilitate mobility and to reduce pain. Therefore, a combination of CDT and other physiotherapeutic measures is recommended, particularly for multimorbid patients with lymphoedema or for patients with posttraumatic lymphoedema.

• Malignant lymphoedema / palliative care situation:
In patients with lymphoedema due to metastasis who are thus affected by an incurable oncological disease, treatment of lymphoedema should be incorporated into the palliative care concept as recommended by the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the World Health Organisation (WHO) (see S3-guideline palliative medicine http://leitlinienprogramm-onkologie.de/Palliativmedizin. 80.0.html) (207-210).

• Posttraumatic and postoperative oedema:
In the case of postoperative or posttraumatic oedema, MLD as a part of CDT should be regularly applied as an additional treatment. During MLD, the anatomy of the individual patient should be taken into consideration. Stimulation of lymphangiomotoricity decreases oedema, facilitates the healing process and reduces the development of postoperative complications, such as lymphoceles, seroma and keloid scars. The healing process is further improved through the reduction of pain. Some patients may also benefit from the application of slightly compressing bandages.

7. What are absolute and relative contraindications of Complex Decongestive Therapy (CDT) or its components?

Absolute contraindications: Decompensated cardiac failure, acute deep leg vein thrombosis, erosive dermatosis, acute severe erysipelas and peripheral arterial occlusive disease stage III and IV.
Relative contraindications: Malignant lymphoedema, skin infections, skin diseases (for instance blistering dermatosis) and peripheral arterial occlusive disease stage I and II. If necessary, patients should be treated on an in-patient basis.

Consent 96.9% (strong consent)

Commentary:

Absolute contraindications

Decompensated cardiac failure: In the case of clinical signs of decompensated cardiac failure, the priority is recompensation by a specialist in internal medicine. Mobilisation of peripheral oedema may put a further strain on the heart (202, 211-213).

Deep leg vein thrombosis:
Because acute deep leg vein thrombosis may lead to pulmonary embolism, initiation of manual lymphatic drainage should depend on the angiological or phlebological diagnosis, whereas compression therapy is indicated in such patients.

Erysipelas:
Systemic treatment with antibiotics is indicated in the case of erysipelas. Depending on the patient's general state of health and condition of the skin, CDT should be discontinued on the affected extremity until the antibiotic treatment takes effect.

Erosive dermatosis:
CDT is contraindicated in the case of extensive erosive dermatosis.

Peripheral arterial occlusive disease stage III and IV:
CDT on the affected extremity is contraindicated.

Relative contraindications
In the presence of relative contraindications, the therapeutic advantages of CDT have to be balanced against the possible side effects of the underlying disease.

Peripheral arterial occlusive disease stage I and II:
In the case of peripheral arterial occlusive disease, possible contraindications should be assessed by means of angiological evaluation prior to CDT, in particular before compression.

Malignant lymphoedema:
CDT should not be conducted in patients with malignant lymphoedema who consider this treatment an additional burden with negative effects on quality of life.

8. What further measures are employed or discussed in the context of treating lymphoedema?

Further measures in the treatment of lymphoedema are (in alphabetical order): Apparative intermitting compression (AIC)/intermitting pneumatic compression (IPC), deep-acting oscillation, diet, lymph tapes, medication (oral and topical), obesity prophylaxis and treatment, soft laser and thermotherapy. However, the available data on these measures are insufficient for making a recommendation in the context of a guideline.

Consent 100% (strong consent)

Commentary:

Apparative intermitting compression (AIC) and intermitting pneumatic compression (IPC):
AIC and IPC may be a type of treatment adjuvant to CDT, particularly in distal lymphoedema of the arms or legs without involvement of the ipsilateral quadrants of the trunk and in the

case of restricted mobility of the patient. Studies have shown that the mode of action of AIC and IPC is to move tissue fluid in the tissue channels toward the centre (68).

Deep-acting oscillation:

During deep-acting oscillation with the HIVAMAT device, a pulsed electrostatic field is built up between the hand of the practitioner or an applicator and the patient. This treatment not only has an anti-oedemic effect but also reduces pain (216-222).

Diet:

From a lymphological point of view, a special diet is only indicated in very rare forms of lymph vessel anomalies with chylous effusions or in the case of lymphostatic protein-losing enteropathy (199). Chylous reflux syndromes require initiation of a diet with reduced long-chain triglycerides, containing medium-chain triglycerides (MCT diet) (68).

Lymph tapes:

For the treatment of lymphoedema, use of elastic tapes instead of compression therapy is not recommended during phase II of CDT. An elastic tape as an additional therapeutic measure underneath a compression stocking does neither reduce the volume of oedema nor the feeling of tightness due to oedema (214, 215).

Medication:

No drugs for the causal treatment of lymphoedema are currently available. Complications of lymphoedema may be treated with the appropriate medication.

Obesity prophylaxis and therapy:

Obesity has a significantly deteriorating effect on lymphatic function and is thus a key risk factor for the development of secondary lymphoedema. Patients with both lymphoedema and obesity are recommended to undergo weight loss therapy according to the guideline of the German Association for the Study of Obesity. For patients with a BMI of more than 40 kg/m², bariatric intervention should be taken into consideration.

Soft laser and thermotherapy:

There is no evidence on the effectiveness of these two methods.

Working group 5: Surgical therapy

Rüdiger Baumeister, G. Björn Stark, Gunther Felmerer, Andreas Frick, Jens Wallmichrath and Nestor Torio-Padron

1. What therapeutic measures should patients with lymphoedema receive before surgery?

Adult patients with lymphoedema should only be offered surgery after having received complex decongestive therapy (CDT) according to approved guidelines in an outpatient or inpatient setting for 6 months.

Consent 96.9% (strong consent)

Commentary:

Because surgical interventions are more invasive than non-surgical measures, it is important to wait for the effects of conservative therapy. Various conservative treatment measures have been evaluated in the respective guideline on lymphoedema. Conservative therapy according to the recommendations of the guideline ensures comparable and sufficient primary therapy. The duration of non-surgical therapy depends on the risk of exacerbating secondary tissue changes with increasing duration of oedema on the one hand and the possibility of regression in the case of transient oedema on the other hand. Because transient oedema has a time frame of approximately 6 months, this period should be chosen as the lower time limit.

2. Under which conditions should surgery become preferable to conservative therapy?

Surgery should be taken into consideration when patients treated with and adhering to conservative therapy according to approved guidelines suffer physical or psychological stress or show increasing secondary tissue changes.

Consent 96.9% (strong consent)

Commentary:

Investigations into quality of life after lymph vessel transplantation indicate that quality of life that has already been increased by means of conservative therapy (223) is further enhanced by reconstructive surgery (224). Patient answers have shown that the time-consuming conservative therapy of lymphoedema represents a significant limitation in the quality of life of working people, who thus seek an alternative to continuous conservative therapy. A major reason for the severe psychological stress, particularly of patients with lymphoedema of the

arms, is stigmatisation because of the visible swelling of the extremities and the visibility of wearing a compression stocking (224-226). These limitations in quality of life affect the private and professional life of patients as well as their physical and mental health.

3. What information do patients require before surgery?

In the context of participatory decision-making, patients should be informed in detail about the different possibilities of surgical therapy with regard to the respective intervention and its effects. Further therapeutic measures that may become necessary after surgery should also be discussed.

Consent 93.8% (consent)

Commentary:

In principle, surgical therapy comprises three different interventions, which are presented in tabular form with regard to the respective intervention and its clinical field of application and proven effects. The most important references in the literature are also included.

Type of surgical intervention	**Clinical field of application**	**Proven effects**
Reconstructive microsurgical intervention		
Microsurgical autogenous lymph vessel transplantation	Secondary and selective primary lymphoedema due to localised disruption of lymph vessels, for instance lymphoedema of the arms after axilla dissection or one-sided leg oedema (a healthy leg is the prerequisite for harvesting lymph vessel transplants)	Clinical studies Prove of long-term patency Long-term volume reduction Prove of normalisation of lymph transport (77, 81, 225-232)
Interposition of autogenous veins	Lymphoedema due to localised disruption of lymph vessels; mostly shortened vein segments because of gauge differences	Case reports (233, 234)
Flap surgery incorporating lymph vessels	Secondary lymphoedema	Case reports (235)

Deviating interventions		
Lymphatic-venous and lymphonodulo-venous anastomosis	Primary and secondary lymphoedema (no additional venous obstruction!)	Clinical studies Long-term volume reduction (236-241)
Autogenous lymph node transplants	Primary and secondary lymphoedema	Clinical studies, case reports (242-244)

Resective procedures		
Liposuction	Primary and secondary lymphoedema Non-pitting lymphoedema Also, as an additional minimally invasive intervention to remove excess secondary tissue after the improvement of lymphatic drainage by reconstructive surgery	Clinical studies Long-term volume reduction under the provision of continuous compression therapy (245, 246) (if increasing the capacity of lymph transport by microsurgical intervention was not possible beforehand) (226)
Resection of skin, subcutaneous tissue, fasciae to a varying extent, direct wound closure or flap procedures or split skin grafts	Primary and secondary lymphoedema	Long-term volume reduction (247) Increasing quality of life (21) Reduction of postoperative complications (248)

Various risks and chances need to be taken into consideration. General risks associated with surgical intervention are infection, bleeding and possible damage to nerves or vessels and thrombosis; however, the specific risk regarding the lymphatic drainage system also needs to be taken into consideration. Prior to the harvest of lymph vessels in the thigh for transplantation, normal lymph flow should be confirmed by sequential scintigraphy. Removal of lymph vessels should exclude the constrictions in the lymphatic drainage system of the leg, inguinal lymph nodes and the bottleneck of the lymphatic drainage system at the inner aspect of the knee. The lymph vessels in the ventromedial bundle at the thigh are dyed by means of an intraoperative injection of patent blue® dye. Besides the grafts, coloured and hence functioning lymph vessels must always remain untouched. Scintigraphic examinations

have shown that the removal of lymph collectors is possible without affecting the lymph flow (249).

A detailed report is available on realised risks of lymph node transplantation including the removal of lymph nodes, for instance in the groin (250).

Resective surgery should be reserved for patients with severe forms of lymphoedema (stage II to III) of the extremities or the genital region. Intensive perioperative CDT helps to significantly reduce surgical risks and postoperative complications of resective surgical procedures (248). Resective surgery at the genital region significantly increases the quality of life of affected patients and significantly decreases the rate of infection due to erysipelas (21).

4. What is the order and priorisation of the different surgical methods for lymphoedema?

The decision on a particular surgical procedure should be mainly focused on the reconstruction of the interrupted lymphatic drainage system or a deviating procedure.

Consent 93.8% (consent)

Commentary:

The majority of lymphoedema in Europe are caused by local disruption of the lymph flow due to medical intervention. Therefore, similar to the established bypass procedures in general vascular surgery, connecting the previously normal lymphatic drainage system before and after the blockage seems to be a logical reconstruction measure for lymphoedema caused by local disruption of the lymph flow (251).

According to the objective data available, the best surgical method is reconstruction of the previously normal lymphatic drainage system. For this reason, evaluating the possibility of reconstruction should be a matter of priority. Evidence on long-term patency has been available for more than 10 years (226, 230). Scintigraphic examinations have shown significant improvement in lymphatic drainage up to normalisation even after more than 7 years (231, 232). Long-term volume measurements have shown significantly reduced volume of the legs after 4 years and of the arms after 10 years (225, 226).

5. What are contraindications to surgical treatment?

Surgery is contraindicated in malignant lymphoedema and in the presence of internistic or anaesthesiologic contraindications.

Consent 87.5% (consent)

Commentary:

Florid malignant diseases that are causal for the development of lymphoedema increase the deterioration of the lymph transport capacity. Such increase would counteract any surgical procedure aiming at enhancing the transport capacity.

With the exception of peripheral lymphatic-venous anastomosis, which may also be conducted in local anaesthesia, the described surgical procedures need to be carried out in general anaesthesia. In this respect, the guidelines of the German Society of Anaesthesiology should be observed, which describe the justifiability of anaesthesia in relation to surgical intervention.

Working group 6: Primary prevention of lymphoedema

Martha Földi, Ute-Susann Albert, Susanne Helmbrecht, Sebastian Jud, Vesna Bjelic-Radisic, Gerson Strubel, Hans Ortmann and Stephan Wagner

Introduction

Prevention is not only important with regard to the development of lymphoedema but also over the course of the disease.

The following issues need to be differentiated:

- The time point of preventive measures in disease development and disease progression,
- The objective of preventive measures,
- The type of lymphoedema (primary versus secondary lymphoedema), and
- The type of preventive measure.

Definition: Prevention

According to Caplan (252), there are three types of prevention: primary, secondary and tertiary prevention.

Primary prevention

Primary prevention measures are started **before** the onset of clinical disease symptoms. Thus, the aim of primary prevention is to avoid the development of a disease by employing appropriate prevention measures. With regard to lymphoedema, primary prevention measures are aimed at patients at risk of developing lymphoedema or at patients with lymphoedema in the stage of latency, for instance oncological patients who have received interventions with a possible effect on the lymphatic drainage system.

Secondary prevention

Secondary prevention measures are started at the early stage of a disease and are aimed at preventing the progression and chronification of a disease. With regard to lymphoedema, secondary prevention is highly important particularly for patients with lymphoedema stage I. Early-stage lymphoedema necessitates adequate and consequent lymphological therapy in order to prevent progression and chronification of the disease. Thus, the boundaries between secondary prevention and therapy of lymphoedema are fluent.

Tertiary prevention

Tertiary prevention measures are aimed at preventing both the deterioration of a disease and the development of any complications. Tertiary prevention is aimed at patients with manifest diseases, chronic diseases and rehabilitants. Therefore, tertiary prevention is used in patients with chronic lymphoedema. The aims of tertiary prevention measures are the prevention of erysipelas and lymphological long-term damage.

Objective of this guideline chapter

This guideline chapter is exclusively about the primary prevention of lymphoedema. Measures of secondary and tertiary prevention coincide with the treatment measures of both primary and secondary lymphoedema, which are described in the respective chapter of the current guideline (see chapters 4 and 5).

A key factor of primary prevention is informing affected patients on the nature of the disease lymphoedema, its early symptoms and the appropriate behaviour and lifestyle. Furthermore, therapeutic measures may also be employed in the primary prevention of lymphoedema (see chapter 4).

Primary prevention of primary lymphoedema

1. What measures should be employed in people with a family history of primary lymphoedema?

People with a known risk of developing primary lymphoedema should be informed in detail about the risk of developing the disease, additional risk factors and the types and symptoms of lymphoedema. Relevant diseases should be treated by a specialist.
There are no specific measures for the primary prevention of primary lymphoedema.

Consent 100% (strong consent)

Commentary:

People with a predisposition to primary lymphoedema, for instance in the case of a family history of primary lymphoedema, should be informed about their risk of developing the disease and the nature of the disease lymphoedema. Affected people should lead a healthy lifestyle and avoid becoming overweight. Diseases affecting the lymphatic drainage system such as diabetes mellitus, thrombosis, venous insufficiency and malignant tumours should be treated according to the respective guidelines. No study has yet investigated whether the use of specific primary prevention measures in patients with primary lymphoedema prevent the clinical manifestation of lymphoedema.

Primary prevention of secondary lymphoedema

Secondary lymphoedema develops as a result of acquired restriction in the function of the lymphatic drainage system. Of particular importance in this context is the influence of the treatment of malignant tumours on the lymphatic drainage system, above all lymphadenectomy and radiation treatment. Apart from oncological interventions, the lymphatic drainage system may also be influenced by surgical interventions for other indications.

2. What type of oncological management should be selected for the primary prevention of secondary lymphoedema?

If justifiably and safe from an oncological point of view, the oncological therapeutic option with the least impact on the lymphatic drainage system should be selected with regard to the primary prevention of secondary lymphoedema.

Consent 100% (strong consent)

Commentary:

With regard to oncological therapeutic options, reference is made to the respective oncological specialist guidelines. From the lymphological point of view, the guideline-based oncological treatment option with the least impact on the lymphatic drainage system should be chosen for each patient. This recommendation applies to both oncosurgical procedures, for instance the preferable surgical intervention of sentinel lymphadenectomy versus primary radical lymphadenectomy, as well as to other oncological treatments such as radiotherapy (16, 30, 253-255).

Furthermore, it seems advisable to pay attention to the anatomy of the lymphatic drainage system when choosing the type of incision and surgical technique. The same applies to the choice of incisions in vascular surgical interventions (256). However, no literature reports are available yet on the type of surgical incisions and preparation with regard to the primary prevention of lymphoedema.

In the context of primary prevention of lymphoedema, oncological treatment should ideally involve as few complications as possible. Both clinical observations as well as individual studies have indicated that the development of complications, such as wound infection with secondary healing, haematoma, seroma and radiogenic skin damages, are associated with an increased risk of developing lymphoedema (257-259). The reason for this increased risk may be impaired regenerative capacity within the lymphatic drainage system after surgery.

3. How can people at risk of developing lymphoedema be identified so that they may be treated at an early stage?

Next to risk stratification, the basis for early diagnostics and observation is pre-interventional and post-interventional measurement methods, such as measuring volume and/or circumference, which always need to be conducted with the same technique and documented. History taking should include complaints such as feeling of tightness of the skin, swelling and functional restrictions.

Consent 96.9% (strong consent)

Commentary:

If possible, people at risk of developing lymphoedema should be identified by means of risk stratification. For instance, risk factors for the development of secondary lymphoedema of the arm after breast cancer treatment are obesity, axillary lymphadenectomy (versus sentinel lymphadenectomy only), postoperative radiation therapy, wound infection, systemic therapy with taxanes and young age (260-265). All interventions bearing the risk of developing lymphoedema should be assessed in the context of routine pre-therapeutic preparation or during regular follow-up examinations. The key feature in this context is the application of standardised assessment methods and appropriate documentation (74, 266).

Patient answers of questions regarding limitations of quality of life have correlated with objective functional limitations and measurements of circumference (267, 268). Thus, patients should be motivated to pay attention to their symptoms and should be asked about their observations with regard to feeling of tightness of the skin, swelling and functional limitations.

4. May manual lymphatic drainage (MLD) be used for the primary prevention of secondary lymphoedema?

In the context of primary prevention of secondary lymphoedema, patients with a high risk of developing lymphoedema (at the stage of latency) can receive manual lymphatic drainage therapy, which should ideally be started within the first days after an intervention affecting the lymphatic drainage system, such as lymphadenectomy.

Consent 100% (strong consent)

Commentary:

Two prospective randomised clinical studies are available, investigating the use of manual lymphatic drainage (MLD) for preventing secondary lymphoedema after breast cancer treatment. In one study, female patients in the treatment group received MLD for the first 3 weeks after surgery as well as information material on lymphoedema. Female patients in the control group were only given the information material. The study showed that the use of MLD in the first 3 weeks after surgery had a significant benefit regarding the prevention of secondary lymphoedema (269). In another study, patients in the treatment group received MLD for 6 months; treatment started 5 weeks after axilla dissection. The control group were treated with general physiotherapy. Both groups also received information material on lymphoedema. In this setting, MLD did not have any benefits regarding the prevention of lymphoedema (176).

The available studies indicate a positive effect of MLD on primary prevention, particularly if therapy is started in the early postoperative phase. However, the optimal duration of primary preventive MLD is still unclear. It is also not yet known what patients will benefit from MLD therapy. The best time to start treatment is also unclear, just as the appropriate intensity of

the treatment. Moreover, no data are available allowing the deduction of risk stratification (for instance after radical oncological therapy and concomitant diseases exacerbating lymphoedema), which − if necessary − could modify the primary preventive use of MLD. Studies have indicated that the risk of developing lymphoedema may be reduced by specific physiotherapeutic exercises in combination with early information on the risk of developing lymphoedema and corresponding behavioural recommendations (270).

5. Should lymphological compression measures be used in the primary prevention of secondary lymphoedema?

No evidence is available on the benefit of lymphological compression measures such as bandages or medical compression stockings for the primary prevention of secondary lymphoedema.

Consent 100% (strong consent)

Commentary:

The feasibility and effectiveness of medical compression stockings for the primary prevention of secondary lymphoedema after lymphadenectomy have been investigated in two studies (271, 272), which included patients with a history of inguinal lymphadenectomy because of vulvar cancer or malignant melanoma. None of the two studies showed any significant effect of lymphological compression measures with regard to reducing the risk of developing secondary lymphoedema of the leg.

6. Are physical activity and sports important factors for the primary prevention of secondary lymphoedema?

Patients at risk of developing lymphoedema should stay physically active and participate in sports. Physical activity should be professionally monitored, at least at the beginning, and should be adjusted to the individual level of fitness. Overexertion and injuries should be avoided.

Consent 100% (strong consent)

Commentary:

The positive effects of physical activity are proven, particularly for oncological patients, not only with regard to their general health but also in the context of quality of life (273, 274). Physical activity even has a positive effect on the oncological prognosis (275, 276). The clear benefit of physical activity for oncological patients – for both patients at risk of developing lymphoedema as well as for patients with already manifest lymphoedema − led to the question whether physical activity also influences the risk of developing secondary lymphoedema or whether lymphoedema is exacerbated by the activity.

The question about the influence of sports activity on the risk of developing secondary lymphoedema has been investigated in several clinical studies including female patients with breast cancer and in a meta-analysis of 4 randomised studies. No effect increasing the risk of developing lymphoedema could be found in any of the studies, in which both perseverance and strength were tested in the early phase after breast cancer (277).

In patients who had already developed secondary lymphoedema, physical activity had no negative effects on the course of the disease, or, in other words, there was no deterioration of lymphoedema (185, 278-286). Moreover, there are several indications that physical activity may prevent the development of lymphoedema (287, 288). It should be noted, however, that no studies are yet available indicating optimal training programmes and training intensity or the best time to start training after lymphadenectomy. Stratification regarding various risk groups is also missing.

Overall, the authors suggest that oncological patients should be motivated to engage in sports activity. With regard to the risk of developing lymphoedema, patients should be informed that they should work out according to their level of fitness and avoid injury and overexertion. Ideally, the training programme should be professionally monitored and gradually increased.

7. Should complex decongestive therapy (CDT) be used for the primary prevention of secondary lymphoedema after interventions affecting the lymphatic drainage system?

Complex decongestive therapy (CDT) should not be used for the primary prevention of lymphoedema because of the current lack of evidence on the benefit of the combined use of all five components of CDT.

Consent 100% (strong consent)

Commentary:

Only the individual components of CDT − but not the components in their entirety − have been investigated in the framework of clinical studies with regard to the prevention of lymphoedema in patients at risk of developing lymphoedema due to oncological intervention (see chapter 4). For the prevention of lymphoedema, the individual components evaluated so far are manual lymphatic drainage and compression therapy, partly supplemented by other physiotherapeutic measures, sports and/or information on lymphoedema (289). For this reason, no recommendation can currently be made for the combined use of MLD, compression therapy, decongestive therapy, skin care or skin regeneration and patient information for the primary prevention of lymphoedema.

8. Should apparative intermitting compression therapy (AIC, pneumatic compression) be used for the primary prevention of secondary lymphoedema?

Apparative intermitting compression therapy (AIC) should not be used for the primary prevention of secondary lymphoedema.

Consent 100% (strong consent)

Commentary:

This method has not yet been examined for the primary prevention of secondary lymphoedema. From the authors‘ point of view, there is no indication for using AIC in this context.

9. What is the role of patient information and education in the primary prevention of secondary lymphoedema?

Patients should be informed about their risk of developing lymphoedema as well as about the various types of lymphoedema, the different forms of clinical manifestation and the possible courses of the chronic disease lymphoedema. Recommendations on specific behaviour to minimise the risk of developing lymphoedema should be provided individually and comprehensively to further the personal responsibility of patients.

Consent 100% (strong consent)

Commentary:

Information and education play a key role in the disease lymphoedema (290-292). Patients should be informed about their risk of developing lymphoedema as well as about the various types of lymphoedema, the different forms of clinical manifestation and the possible courses of this chronic disease. Patients should be made aware that they have a compensated condition in the sense of a balance between the amount of lymphatic loads and the residual function of the lymphatic drainage system and that they may influence this balance through their behaviour. The aim is to further the personal responsibility of patients regarding the primary prevention of lymphoedema: Behavioural patterns increasing the lymphatic loads and/or further decreasing the transport capacity of the lymphatic drainage system should be systematically avoided in the long run.

10. Should medical interventions in areas of the body with (potentially) impaired lymphatic drainage be avoided in patients at risk of developing lymphoedema?

If reasonable alternatives are available, no medical intervention should be conducted at an extremity affected by lymphoedema or at an extremity at risk of lymphoedema, for instance at the equilateral arm after axillary lymphadenectomy because of breast cancer.

Consent 100% (strong consent)

Commentary:

Medical interventions such as venepunctures, injections and infusions as well as the application of a blood pressure cuff or surgery bear the risk of increasing the lymphatic loads and/or further reducing the remaining lymph transport capacity in areas of lymphatic congestion through trauma or infection. Therefore, such interventions may trigger the initial manifestation of secondary lymphoedema or may lead to the deterioration of already present lymphoedema. The literature reports available on these interventions, however, are partly inconsistent (293-296).

Nevertheless, the authors suggest that alternatives to interventions in areas of potential lymphatic congestion should be chosen whenever possible, for instance blood sampling and infusions should be done at the contralateral extremity. Intravenous catheter systems (ports) should be implanted at the contralateral side, thus in the quadrant of the trunk lying outside the potential lymphatic congestion area.

Indications for surgical interventions in lymphatic congestion areas should be carefully and individually assessed for each patient. Where applicable, patients should present to a specialist in lymphology prior to the intervention. Patients should be informed about the potential risk of developing lymphoedema or the deterioration of already present lymphoedema before each elective surgical intervention in a (potential) lymphatic congestion area.

Working group 7: Psychosocial aspects of lymphoedema

Ute-Susann Albert, Walter Döller, Franz Flaggl, Susanne Helmbrecht and Christian Ure

The ‘International Classification of Functioning, Disability and Health‘ (ICF) of the World Health Organisation (WHO) and the derived theory model of rehabilitation are a generally recognised basis for comprehensively understanding patient treatment by now (297, 298). The aim of rehabilitation is improving or restoring patient participation, which refers to the participation in private, professional and social life in the respective cultural and social context. However, there is no direct link between a health problem and the intended participation. The health problem needs to be mastered primarily by the patient (299) (Figure 1).

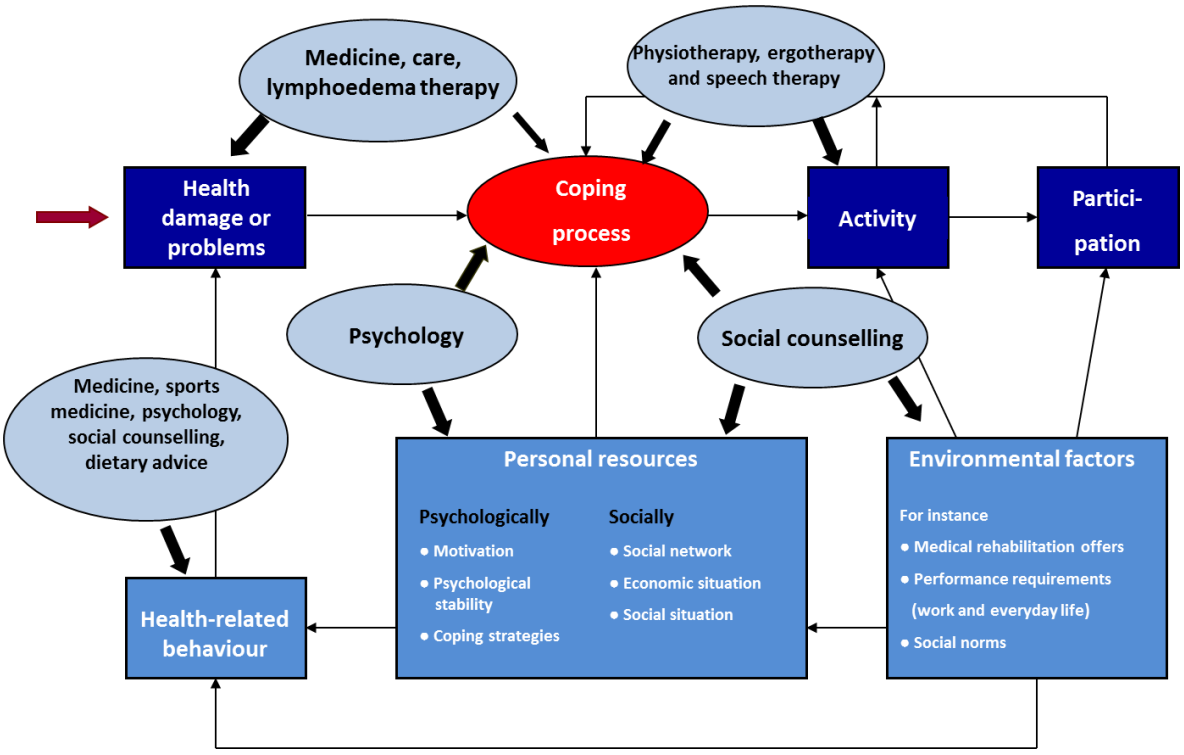

Fig 1: Theory model of rehabilitation, Gerdes, N. & Weis, J. (2000)

As a chronic disease, lymphoedema changes the life situation of affected patients, which requires multiple adjustments. Important factors apart from the physical disease itself are the psychological and social impact of the disease. Furthermore, the reduced functional ability makes mastering daily tasks in the family and at work difficult and requires therapeutic measures to investigate needs and address individual coping resources.

Special characteristics in comparison to other chronic diseases

- Just under one third (30.3%) of 310 examined rehabilitants are psychologically unaffected at the start of lymphological rehabilitation. About one third (34.5%) of the patients show increased psychological distress, and in about one third (35.2%) of the patients the degree of psychological distress requires treatment (300).
- Female patients with cancer and lymphoedema are more anxious and more prone to depressive states of mind than female patients with cancer but without lymphoedema (300).
- Not only quality of life but also the body concept is significantly worse in patients with lymphoedema than in patients with acute but temporary physical impairment (301).
- Assessments of quality of life of patients with lymphoedema are mainly available for women with secondary lymphoedema after breast cancer treatment. These studies have shown that female patients with lymphoedema have significantly reduced quality of life with regard to physical functional ability, physical role function, pain, general self-perceived health, vitality, social function, emotional role function and psychological well-being (302, 303).
- The multi-professional setting of in-patient rehabilitation including exercise therapy and treatment of lymphoedema significantly improves outcome for patients with breast cancer and lymphoedema regarding lymphoedema of the arm, overall quality of life, physical and emotional function, feeling of tiredness and breast pain (75).

Why is complementary psychological treatment sensible and necessary?

Psychologically distressed patients with lymphoedema who receive psychological treatment show significantly better rehabilitation results than psychologically distressed patients without such treatment. Complementary psychological treatment within the 3-week period of inhouse rehabilitation consisting of at least two interventions of 50 minutes each significantly improves the mental state and decreases the pressure due to physical complaints. It should be emphasised that such treatment can result in long-term improvement of up to 7 months (304).

Implications for practice

- The multi-professional and interdisciplinary treatment of patients is based on the ICF and the derived theory model of rehabilitation (75, 297-299).
- Screening procedures for psychological distress may already be used for monitoring at the start of therapy and over the course of the treatment. Validated screening tools are, among others, the Hospital Anxiety and Depression Scale (HADS questionnaire) and the distress thermometer (see S3 guideline Psycho-oncological Diagnostics, Counselling and Treatment. Guideline register of the Association of the Scientific Medical Societies in Germany [AWMF] 032/51OL. version 1.1) (305). Furthermore, more comprehensive and

validated survey instruments are available for recording subjective impairment through physical and psychological symptoms, for instance, the symptom checklist SCL-90-R (306), the Giessen Complaint Questionnaire GBB (307), the EORTC QLQ-C30 questionnaire with modules for the different organs for patients with cancer (html://www.EORTC.org) and specific questionnaires for patients with lymphoedema of the lower limbs (Lymph-ICF-LL) (308).

- Psychologically distressed patients with lymphoedema benefit from psychological intervention in the setting of inpatient rehabilitation treatment, for instance the service catalogue of the statutory pension insurance scheme in Germany (Rentenversicherung Bund) and clinical psychological therapy in the framework of lymphological inpatient rehabilitation in the service catalogue of the social insurance agencies in Austria.
- Each patient with lymphoedema should be informed about psychosocial consultation offers and contact addresses of self-help groups.
- A combination of patient education in health competence and self-management programmes, for instance INSEA/EVIVO (309), may contribute to improving the quality of life of patients with lymphoedema.

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Further references are available online at:
www.dglymph.de
www.lymphologie.org

Attachment: Check list for basic diagnostics (history taking – inspection – palpation and evaluation)

1) Check list for history taking

I) General history

- Family history
    - Is there a family history of lymphoedema?
    - Is there a family history of chronic leg oedema?
- BMI (body height and weight)
- WHR (waist-to-hip ratio)
    - Weight gain (24)
- Surgical interventions (vascular, oncological, orthopaedic and other interventions)
- Pre-existing diseases
    - Metabolic diseases
    - Hormonal diseases
    - Renal diseases
    - Liver diseases
    - Cardiac diseases
- Venous and arterial diseases
- Past inflammatory processes
    - Erysipelas
    - Erythema
    - Tick bites and bites by other insects
- Any oversea stays in the past few months or years? Any stays in the tropics?
- Oncological history
    - Affected organ
    - TNM classification
    - Histology
    - Tumour-specific therapy
    - Course of disease (recurrence)
- Immobilisation
    - Have there ever been periods of immobilisation due to, for instance, orthopaedic or neurological diseases?
- Specific questions on vegetative history
    - Weight fluctuations in the course of the day or month (cyclical weight gain)

    - BMI (body height and weight) and WHR (waist-to-hip ratio) (disproportional fat distribution)
    - Any connection with menstrual cycle?
- Accidents
    - Soft tissue injuries
    - Fractures requiring surgical intervention
- Intake of medication
    - Diuretics
    - Chemotherapy
    - Neurotropic medication such as dopamine agonists or GABA-agonists
    - Hormonal drugs (corticoids, oestrogens, gestagens and rGH)
    - Ca antagonists
    - Glitazone (if necessary, in combination with insulin)
    - And others (see reference (15))

II) Specific history taking of oedema

Patient-reported outcomes (patient-relevant outcomes)

Symptoms associated with lymphoedema (not at all, little, moderate, very)*

- Swelling
- Pain
- Limited function and mobility
- Feeling of tightness of the skin
- Feeling of heaviness
- Feeling of tightness regarding clothing, shoes and jewellery
- Skin changes

** Data may be collected by means of validated questionnaires, for instance with the quality of life questionnaire EORTC-BR 23 (breast module 23) for female patients with breast cancer. This questionnaire on symptoms of lymphoedema of the arms and breast is available in 81 languages: www.**eortc**.be/qol/downloads/QLQC30/select.asp*

- Time sequence of the development of oedema
    - Onset of oedema
    - Bilateral onset of oedema
        - If yes, symmetrically or asymmetrically
    - Duration of the reversible stage
    - Does the disease progress (slow or fast)?
    - When did the disease progression start?
    - Triggering factors or events
    - Triggering factors (heat or orthostasis)

- Is the oedema generalised, peripheral or central?
- Primary site of peripheral oedema (distal or central)
- Direction of proliferation (centripetal or centrifugal)
- Susceptibility to hematoma
- Frequency of erysipelas
- Lymphorrhoe
- Lymphatic cysts
- Ulcerations
- Lymphological pre-treatments
- Wearing of lymphological compression stockings

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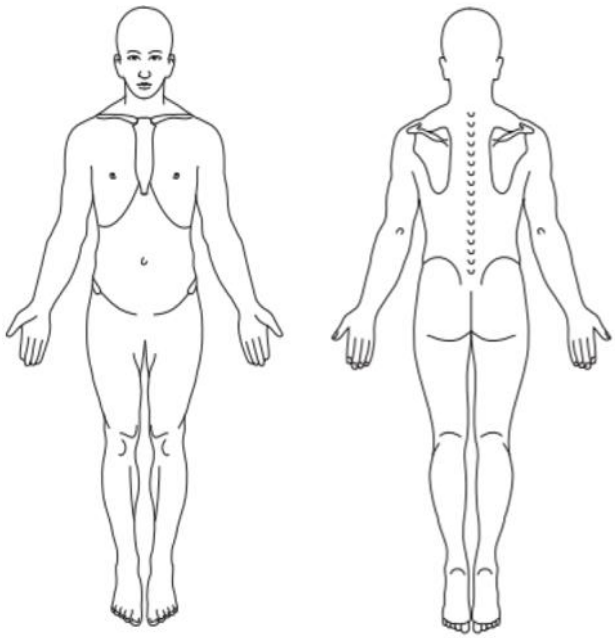
2) Check list for inspection

- Unilateral or bilateral swelling
- Symmetrical or asymmetrical swelling
- Length difference between the extremities (hemihypertrophy)
- Site of swelling
  - Symmetrical swelling of the trunk
    - Shoulders, neck and chest with pain (Dercum's disease)
    - Shoulders, neck and chest without pain (Madelung's disease)
  - Asymmetrical swelling of the trunk
    - Lipohypertrophy
  - Asymmetrical swelling of other sites: (please delineate site)



- Skin condition
    - Colour
    - Trophic skin disorders and hairiness
    - Ulcerations
    - Pigmentation (in children alterations in pigmentation and naevus flammeus)
    - Scars
    - Papillomatosis cutis lymphostatica
    - Erythema (erysipelas, erythrodermia, dermatosis and dermatitis)
    - Hyperkeratosis
    - Ectatic lymphatic vessels of the skin
    - Lymphatic cysts
    - Lymphatic fistulae
    - Rough skin texture
    - Skin changes indicating fungal infection
    - Deepened natural skin folds
    - Syndactyly
    - Skin changes of venous origin (varicosities, phlebitis, corona phlebectatica paraplantaris and blowout phenomenon)

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3) Check list for palpation

- Lymph nodes
    - Enlarged
    - Soft
    - Taut
    - Rough
    - Immobile
    - Movable
    - Tender to the touch
- Arterial status
    - Palpable pulses
    - Frequency
    - Rhythm
- Venous status
    - Venous filling index, varicosities, corona phlebectatica paraplantaris and blowout phenomenon
    - Signs of phlebitis (pressure pain, hardening, overheating and suspected thrombosis)

- Consistency and pliability of oedema
    - Pasty and soft
    - Taut and elastic
    - Rough and fibrotic
    - Hard and indurated
- Subfascial oedema (pain due to calf compression)
- Expressible lymphatic cysts
- Skin temperature (comparison between the healthy and the affected side upon palpation)
- Possibility to pinch and lift a skinfold, Stemmer's test (if applicable, measuring the thickness of dermal skinfolds)
- Pinching test at the thigh (pressure and pain during pinching)
- Functional test of mobility (range of motion)
    - Shoulder–arm–hand (range of motion, clasping the hands behind the waist and neck and clasping hands behind the neck)
    - Hip–knee–foot

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4) Check list for evaluating basic diagnostics

- Lymphoedema (initial manifestation and follow-up diagnostics)
- Stage of lymphoedema
- Special features (diagnostics and pre-treatment)
- Clinical assessment of participation in professional and social life according to ICF
    - Participation in professional life (unlimited, possible to a limited extent, not possible)
    - Participation in social life (unlimited, possible to a limited extent)
- Advanced diagnostics recommended

Documentation (check list) and archiving of the following results is recommended:

- Volume measurement (Kuhnke perometer)
- Circumference measurement with documentation of body site and difference in sides
- Skin temperature (difference upon palpation)
- Photo documentation

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