



**Kanserde Destek Tedaviler ve Palyatif Bakım Sempozyumu**

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# Onkoloji Hastasında Lenfödem Yönetimi



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**Tanımı:** Lenfatik sıvının birikmesi sonucu ortaya çıkan inflamatuvar bir durumdur.

- Primer ; lenf damarlarının veya düğümlerinin malformasyonu ya da travmaya bağlı kronik lenfatik sistem aşırı yükü nedeniyle
- Sekonder ; sıklıkla kanser ve tedavileri sonucu oluşabilir.



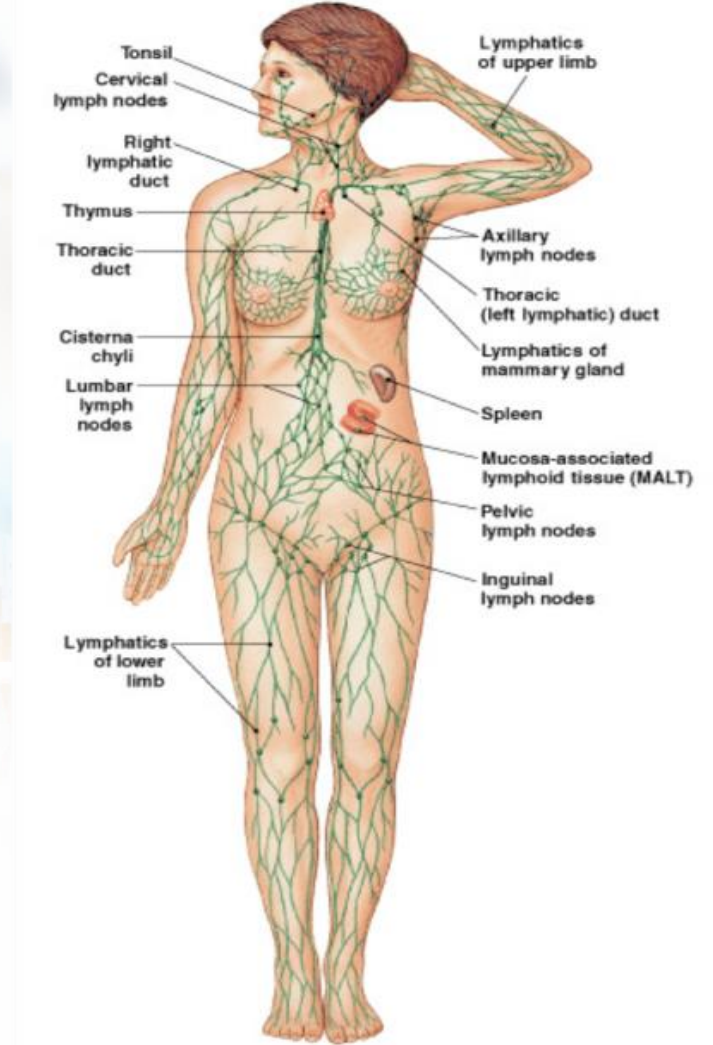


## Lenfatik sistem ; 20 Litre ortalama lenfatik sistemde sirkülasyon

- 16 L lenfatik dolaşımda lenfatik kanallardan geri emilen
- 3-4 L dokulara sızan ve lenfatikler tarafından geri kazanılan

## Lenfatik sistemin ana fonksiyonları

- Vücuttaki sıvı dengesi ,dolaşım sistemine yardımcı (**Dolaşım sistemi**)
- **Sindirim sistemine** yardımcı (yağları kanalize eder)
- **İmmün sisteme** yardımcı
- Hücresel atık ürünlerini ortadan kaldırılması. (**Boşaltım Sistemi**)



- Lenfödem görülme sıklığı % 6 – 30

- “The brawn arm” Handley, The Lancet 1908.

Tedavi edilmemiş ileri evre meme kanserinde kolda şişmeyi tarif etmiş.

- “Elephantiasis chirurgica—its cause and prevention” Halsted, Bull John Hopkins Hosp 1921.

Radikal mastektomi sonrası kolda ödemi tarif etmiş.



- Kanserlin yeri ve tedavi türleri kansere baęlı lenfödem insidansını etkiler.
- Farklı maligniteler için tahminler %5 ile % 83 arasında deęişmektedir.
- Prevalansının yüksek olması nedeniyle meme kanseri sekonder lenfödemlin en sık neden
- Melanom , sarkom , baş boyun tümörleri ve jinekolojik kanserler meme kanserinden sonra
- Kanada da 300.000 kanser hastasını etkiledięi rapor edilmiş.

# Kansere baęlı lenfödem

- Lenfatik kanalların veya düęümlerin tümör tarafından tıkanması
- Lenfatik tümör hücresi infiltrasyonu damarlar (yani lenfanjitik karsinomatozis)
- Lenf düęümü diseksiyon veya çıkarma
- Radyoterapiden kaynaklanan lenfatik kanal hasarı
- Taksan gibi kemoterapi ajanları.

# Lenfödem neden önemli ?

- Yaşam kalitesini bozuyor ( **Quality of life , QoL** )
- Selülit riski 70 kat artıyor.
- Yara iyileşmesinde gecikme doku bütünlüğünde bozulma
- İmmun hücrelerin transportunda bozulma sekonder enfeksiyonlarda artış.
- Kollajen yapımı stimüle olur , protein ve glikozaminoglikanlar cilt altı dokularda birikir ; fibrosiz..
- Kas iskelet sisteminde mobilite sorunları.
- DVT riskinde artış..

# Risk faktörleri:

## Upper limb or trunk lymphedema

- Axillary lymph node dissection
- Radiotherapy to the breast
- Radiotherapy to lymph nodes (axillary, internal mammary or subclavicular lymph nodes)
- Chemotherapy (taxanes)
- Skin changes following axillary radiotherapy (fibrosis, radiodermatitis)
- Complications from wounds or drains
- Axillary web syndrome
- Lymphocele
- Advanced cancer
- Overweight or obese status
- Cellulitis and inflammatory skin conditions
- High blood pressure
- Procedures such as pacemaker insertion and arteriovenous shunt for dialysis
- Filariasis

## Lower limb lymphedema

- Lymphatic vessel compression due to tumour location (pelvic or abdominal tumours)
- Inguinal or pelvic lymph node dissection
- Pelvic radiotherapy
- Deep vein thrombosis and post-thrombotic syndrome
- Comorbid conditions (cardiac or renal disease)
- Advanced cancer
- Overweight or obese status
- Chronic venous insufficiency
- Varicose vein treatments (stripping)
- Cellulitis and inflammatory skin conditions
- Orthopedic surgery
- Prolonged limb immobilization
- Genetic predisposition
- Filariasis

## Head and neck

- Surgical neck dissection
- Radiotherapy



- Lenfödem kalıcı olması ile; kronik inflamasyon
- Cilt Hipertrofisi , fibrosiz
- Tekrarlayan yumuşak doku enfeksiyonu
- **Lenfanjiosarkom (Stewart-Treves Sendromu)**





# Tanı : Öykü ve Fizik Muayene yeterli..

**Dermatologic examination.** This is an assessment of skin integrity, including the presence of dryness, erythema, pachydermia, and hyperkeratotic appearance (verrucous and vesicular lesions). Evidence of lymphorrhea and underlying fungal infection or open wounds secondary to chronic diseases such as diabetes should also be noted.

**Pitting test.** Application of firm pressure to the edematous tissue is done for at least 30 seconds. Skin indentation after release indicates pitting edema, which can be mild or more pronounced in any lymphedema stages. In advanced stages, however, pitting is usually less pronounced due to pachydermia and fibrosis.

**Stemmer sign.** Pinching of skin at the base of the second toe or finger assesses for thickened skin fold. Difficulty in lifting the skin indicates a positive Stemmer sign, which can be present at any lymphedema stage.

**Vascular examination.** This test documents presence of varicose veins and signs of chronic venous insufficiency. For lower limbs, evaluation of pedal pulses is advised if peripheral arterial disease is suspected, as compression therapy is contraindicated in this disease.

Limb volume difference should also be determined by measuring the circumference of both affected and unaffected limbs at different anatomical landmarks. Head and neck landmarks are also used to perform measurements. Serial measurements, which are typically performed by a trained therapist, aid in assessing lymphedema evolution and treatment response but are not mandatory in diagnosing lymphedema.

Although imaging is not routinely used for lymphedema diagnosis, some investigations may be warranted if another condition is suspected, such as a duplex ultrasound to rule out DVT. If peripheral arterial disease is suspected, ankle brachial index test is relevant, especially if compression therapy is considered. Based on history and examination findings. Lymphedema diagnosis is clas-

- Cardinal signs: location, quality, radiation, intensity, severity, alleviating or aggravating factors, and associated symptoms
- Pattern of swelling: insidious versus acute onset, following a trigger event (eg, cellulitis, trauma)
- Nature of swelling: intermittent versus omnipresent
- Identification of nononcologic and oncologic risk factors for lymphedema
- Review of prescribed and over-the-counter medications that may contribute to edema



## Tanısal testler :

Method	Features Measured	Advantages	Disadvantages
<b>Circumference measurement</b>	Circumferential differences using tape measurer	<ul style="list-style-type: none"> <li>Simple and economical</li> <li>To monitor disease progression</li> </ul>	<ul style="list-style-type: none"> <li>Not precise</li> <li>Moderate inter- and intra-operator variability</li> </ul>
<b>Water displacement</b>	Water overflow	<ul style="list-style-type: none"> <li>Reliable and validated</li> <li>Includes hand</li> </ul>	<ul style="list-style-type: none"> <li>No swelling localization information</li> <li>Contraindicated if open wounds</li> </ul>
<b>Perometry</b>	IR scanning with calculation of multiple limb area volumes	<ul style="list-style-type: none"> <li>Rapid measurement</li> <li>Can measure bilateral BCRL</li> <li>Can localize swelling</li> <li>Can detect 3% limb volume change</li> <li>Can measure torso with some models</li> </ul>	<ul style="list-style-type: none"> <li>Expensive</li> <li>Equipment not available everywhere</li> <li>Difficulty with reliable hand measurement</li> <li>Positioning can be problematic</li> </ul>
<b>Bioimpedance spectroscopy</b>	Impedance ratio between limbs Calculates L-Dex ratio	<ul style="list-style-type: none"> <li>Rapid, painless testing</li> <li>Repeatable results</li> <li>Early detection possible</li> </ul>	<ul style="list-style-type: none"> <li>Expensive</li> <li>Limited bilateral limb involvement interpretations</li> <li>Limited to arm and leg use</li> </ul>
<b>3D Laser scanning</b>	Real-time digital 3D image	<ul style="list-style-type: none"> <li>Sensitive to small variations in arm volume</li> </ul>	<ul style="list-style-type: none"> <li>Expensive</li> <li>Arm reference point difficulties</li> <li>Reliability uncertain</li> </ul>
<b>Computed tomography</b>	Skin thickening, honeycombing Fat lobules	<ul style="list-style-type: none"> <li>Objective volume measurement</li> </ul>	<ul style="list-style-type: none"> <li>Expensive</li> <li>Exposure to radiation</li> </ul>
<b>Lymphoscintigraphy</b>	Axillary/elbow lymph nodes Lymphatic ducts Dermal backflow	<ul style="list-style-type: none"> <li>Has been gold standard for diagnosis</li> <li>Shows lymphatic obstruction severity</li> <li>Shows deep lymph flow</li> </ul>	<ul style="list-style-type: none"> <li>Protocol not standardized</li> <li>Potential for poor image quality</li> <li>Little subdermal lymphatic information</li> </ul>
<b>ICG Lymphography</b>	Superficial lymphatic ducts Dermal backflow	<ul style="list-style-type: none"> <li>Detailed visualization</li> <li>Intra-operative measurement</li> <li>No radiation exposure</li> </ul>	<ul style="list-style-type: none"> <li>Limited to lymphatics ~2.0 cm into subcutaneous tissue</li> <li>Not available everywhere</li> <li>Technically demanding</li> </ul>
<b>MR Lymphangiography</b>	Lymphatics Fat deposition Muscle compartments Precise limb volume	<ul style="list-style-type: none"> <li>Gives information on lymphatic function</li> <li>No radiation exposure</li> </ul>	<ul style="list-style-type: none"> <li>Expensive</li> <li>Not available everywhere</li> <li>Technically demanding</li> </ul>

BCRL, breast cancer-related lymphedema; ICG, indocyanine green; IR, infrared; L-Dex, lymphedema index; MR, magnetic resonance

## Lenfödem sınıflaması:

## International Society of Lymphology lymphedema staging definitions

Figure 1. Examples of upper limb lymphedema stages



Figure 2. Examples of lower limb lymphedema stages



### Stage 0

- A subclinical state where swelling is not evident despite impaired lymph transport. This stage may exist for months or years before edema becomes evident

### Stage I

- This represents early onset of the condition where there is accumulation of tissue fluid that subsides with limb elevation. The edema may be pitting at this stage

### Stage II

- Limb elevation alone rarely reduces swelling and pitting is manifest

### Late stage II

- There may or may not be pitting as tissue fibrosis is more evident

### Stage III

- The tissue is hard (fibrotic) and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop



# Etyoloji :

## Neden Sentinal Lenf Nodu Diseksiyonu ?

Aksilla disseksiyonu varlığı lenfödem riskini



Aksilla diseksiyonu genişliği ile direkt orantılıdır.

## SLND sonrası lenfödem % 0-3 NSABP B-32 çalışması

1,278 (MRM - MKC) + ALND

203 Lenfödem

20 den az LND % 14.5

20 - 30 LND % 17.7

30 dan fazla LND % 22.1



## ALND yapılanlarda Lenfödem sıklığı

REFERENCE	NO. OF PATIENTS	MEASUREMENT TECHNIQUE	LYMPHEDEMA INCIDENCE, %
Sackey 2014 <sup>30</sup>	194	Water displacement	45
Sagen 2014 <sup>31</sup>	204	Water displacement	17
Rutgers 2013 <sup>47</sup>	744	NR	28
Ashikaga 2010 <sup>48</sup>	1975	Water displacement	14
Teshome 2014 <sup>49</sup>	853	Circumference	40
Lucci 2007 <sup>34</sup>	445	Circumference	11
Langer 2007 <sup>35</sup>	210	Circumference	19
Francis 2006 <sup>37</sup>	73	Circumference	47
Mansel 2006 <sup>36</sup>	403	Circumference	13
Haid 2002 <sup>43</sup>	140	Circumference	27
Swenson 2002 <sup>44</sup>	78	Subjective	17
Schrenk 2000 <sup>46</sup>	35	NR	57
Total: 12	5354		Average: 28 Range: 11-57 Pooled incidence: 22.3

ALND indicates axillary lymph node dissection; NR, not reported.



## SLND yapılanlarda lenfödem sıklığı

TABLE 1. Studies Assessing Lymphedema After SLNB for the Treatment of Breast Cancer

REFERENCE	NO. OF PATIENTS	MEASUREMENT TECHNIQUE	LYMPHEDEMA INCIDENCE, %
Sackey 2014 <sup>30</sup>	140	Water displacement	20
Sagen 2014 <sup>31</sup>	187	Water displacement	3
Velloso 2011 <sup>32</sup>	45	Circumference	4
Goldberg 2010 <sup>33</sup>	600	Circumference	5
Lucci 2007 <sup>34a</sup>	446	Circumference	7
Langer 2007 <sup>35</sup>	449	Circumference	4
Mansel 2006 <sup>36</sup>	478	Circumference	5
Francis 2006 <sup>37</sup>	26	Circumference	17
Wilke 2006 <sup>38</sup>	2904	Circumference	7
Leidenius 2004 <sup>39</sup>	92	NR	4
Ronka 2004 <sup>40</sup>	57	NR	23
Langer 2004 <sup>41</sup>	40	NR	0
Blanchard 2003 <sup>42</sup>	683	Circumference	6
Haid 2002 <sup>43</sup>	57	Circumference	4
Swenson 2002 <sup>44</sup>	169	Subjective	9
Sener 2001 <sup>45</sup>	303	NR	3
Schrenk 2000 <sup>46</sup>	35	NR	0
Total: 17	6711		Average: 7 Range: 0-23 Pooled incidence: 6.3

SLNB indicates sentinel lymph node biopsy; NR, not reported. <sup>a</sup>Subset of a larger research study which included more extensive nodal surgery.

# Radyoterapi:

**Meme kanseri tedavisinde radyoterapinin uzun takipte en önemli komplikasyonu lenfödemdir.**

- Lenfatik damarlar rölatif olarak radyoresistandır.
- RT sonrası uzun takipte vazokonstrüksiyon görülmektedir ve çevre dokuda oluşan fibrozise ikincil olduğu düşünülmektedir.
- Damarların tersine lenf nodları çok radyosensitifdir ve RT ile fibrozis oluşur.
- Sadece RT
- Sadece ALND
- **ALND + RT % 45 (DİKKAT!!!!)**



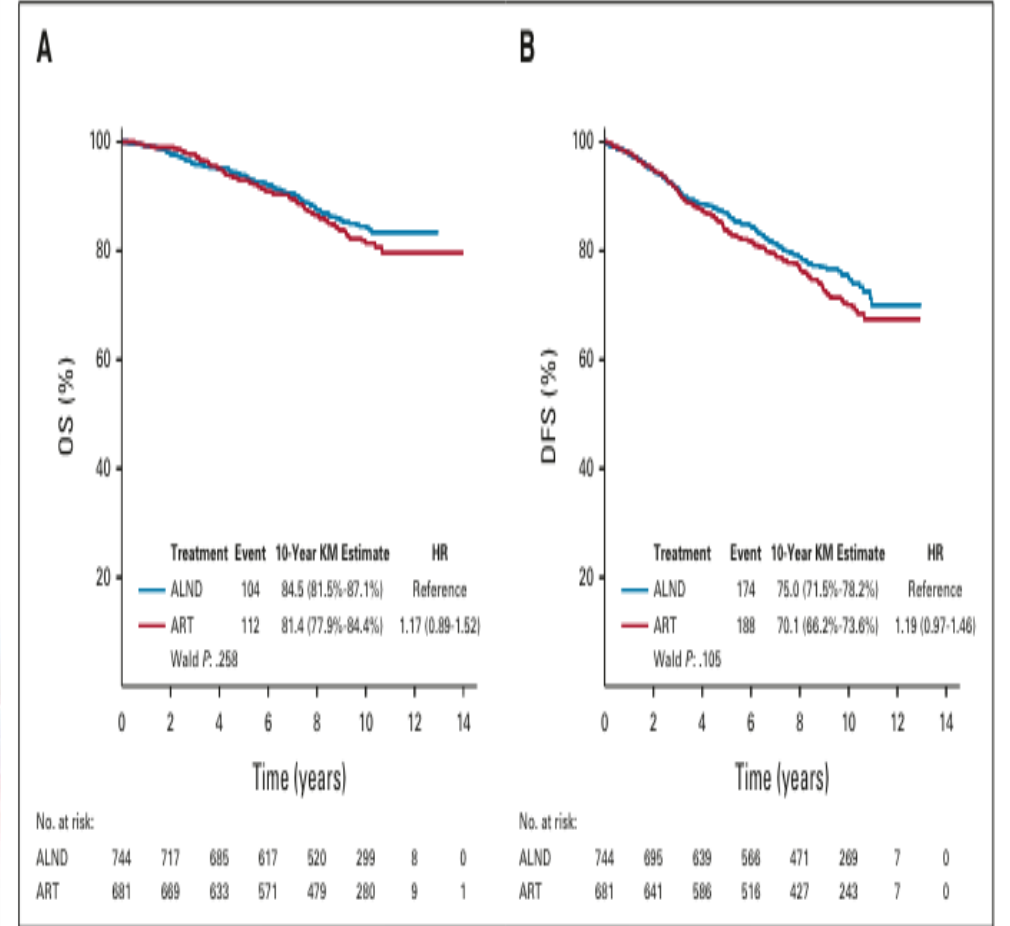


clinical trial updates

## Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial

Sanne A.L. Bartels, MD, PhD, MSc<sup>1,2</sup>; Mila Donker, MD, PhD<sup>2,3</sup>; Coralie Poncet, MSc<sup>1</sup>; Nicolas Sauvé, MSc<sup>1</sup>; Marieke E. Straver, MD, PhD<sup>4</sup>; Cornelis J.H. van de Velde, MD, PhD<sup>5</sup>; Robert E. Mansel, MD, MS<sup>6</sup>; Charlotte Blanken, MD, PhD<sup>7</sup>; Lorenzo Orzalesi, MD, PhD<sup>8</sup>; Jean H.G. Klinkenbijl, MD, PhD<sup>9</sup>; Huub C.J. van der Mijle, MD, PhD<sup>10</sup>; Gard A.P. Nieuwenhuijzen, MD, PhD<sup>11</sup>; Sanne C. Veltkamp, MD, PhD<sup>12</sup>; Thijs van Dalen, MD, PhD<sup>13</sup>; Andreas Marinelli, MD, PhD<sup>4</sup>; Herman Rijna, MD, PhD<sup>14</sup>; Marko Snoj, MD, PhD<sup>15</sup>; Nigel J. Bundred, MD, PhD<sup>16</sup>; Jos W.S. Merkus, MD, PhD<sup>17</sup>; Yazid Belkacemi, MD, PhD<sup>18,19</sup>; Patrick Petignat, MD<sup>20</sup>; Dominic A.X. Schinagl, MD, PhD<sup>21</sup>; Corneel Coens, MSc<sup>1</sup>; Geertjan van Tienhoven, MD, PhD<sup>22</sup>; Frederieke van Duijnhoven, MD, PhD<sup>2</sup>; and Emiel J.T. Rutgers, MD, PhD<sup>2</sup>

**Çalışmada; ALND, analizlerde daha yüksek lenfödem oranıyla ilişkilendirildi. (%24,5'e karşı %11,9; P < 0,001).**



**FIG 2.** (A) OS and (B) DFS. ALND, axillary lymph node dissection; ART, axillary radiotherapy; DFS, disease-free survival; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival.



# Cerrahi sonrasında lenfödem riski

- Yaş
- Tümöral faktörler
- LN durumu
- Pektoralis minor kesilmesi
- Kemoterapi (Taksanlar)
- Postop seroma veya enfeksiyon
- Obesite
- Venöz obstrüksiyon varlığı



# Lenfödem Yönetimi:

Sürekli hasta desteği ve uyum gerektiren bir kronik hastalık yönetim

- Hastaları eğitimi ve tedavi sürecine katılımı
- Etkilenen uzuv hacmini azaltılması
- İşlevsel durumu optimize edin
- Yaşam kalitesinin iyileştirilmesi



# KORUNMA

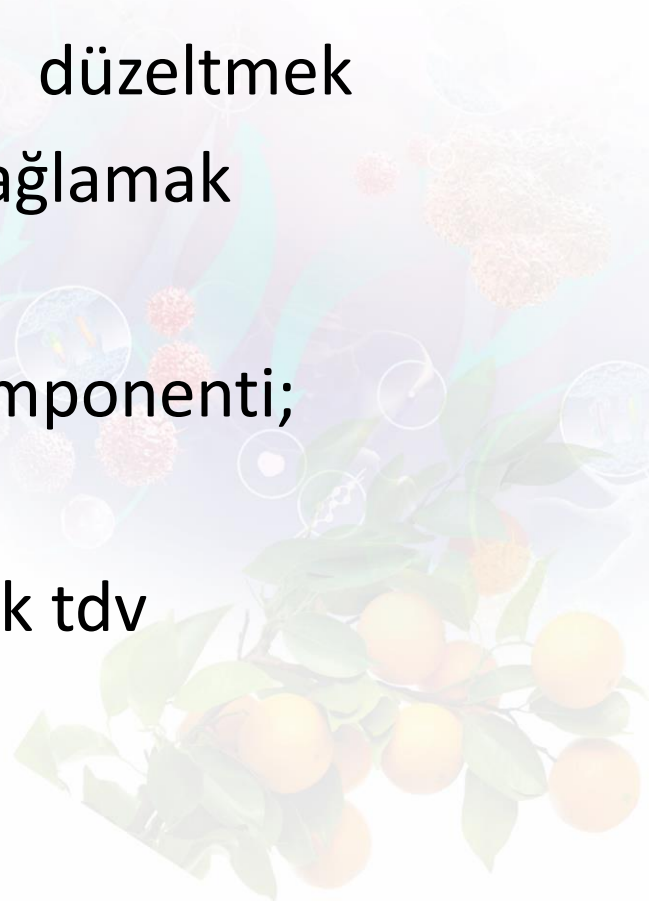
- Kola kan akımını arttıran durumlardan kaçınılmalı; Aşırı egzersiz, aşırı ısı, cilt bütünlüğünü bozan durumlar (enjeksiyon, yanıklar, kesiler)
- Lenfatik kanalları bloke eden durumlardan kaçınılmalı; dar takı ve giyecekler
- Koldan damar yolu açma , tansiyon ölçme gibi etkilenen kolu koruma



# Tedavi:

- 1-Ödemi azaltmak
- 2-Fonksiyonu düzeltmek
- 3-kozmetik sağlamak

- Tedavi 3 komponenti;
- Fizik tdv
- Farmakolojik tdv
- Cerrahi tdv





## 1-Fizik Tedavi :

- Birlikte veya tek olarak; Elevasyon
- Kompresyonlu bandaj
- Masaj
- Özel kol egzersizleri

## Elevasyon :

Otururken ve uzanırken kolun elevasyonu

- Mekanizma bilinmemekte
- Elevasyon ile hidrostatik basınç ve ödem oluşumu azalmakta
- Tek başına elevasyonun yararlı olduğunu dair veri



## **Egzersiz:**

- Kol kompresyon bandajı içinde iken özel egzersiz
- Lenfatik akımı ve protein absorpsiyonunu arttırır.
- Fizik tıv uzmanı denetiminde kişiye özel program yapılmalı

## **Kompresyon:**

- Lenfödem tıv temel yöntemlerinden
- Kompresyon basıncı 20-60 mmHg olmalıdır.
- Ödem oluşumunu azaltır ve kolda lenfatik sıvının drenajına yardımcı olur
- Sadece kol için olanlar elde şişmeye neden olur.
- Günlük 6 saat kullanım faydası bilimsel olarak saptanmıştır.
- Gün içinde, egzersiz yaparken ve seyahatte kullanılmalıdır.

# KOMPRESYON

- Pnömatik Pompalar
- Bazı çalışmalar ile etkinliği saptanmıştır
- Basınç, sıklık ve süre konusunda konsensus yok

## Terapist Tarafından Kompresif Bandaj Uygulaması



## Pnömatik Pompalar







# Kompresyon tedavisi:

<b>Diagnosis: right or left upper limb lymphedema</b>	
<input type="checkbox"/> Multi-layer bandage kit for reduction therapy	
<input type="checkbox"/> Compression garment(s) for daytime use:	
<input type="checkbox"/> Sleeve, class:	<input type="checkbox"/> 15-20 mm Hg or 15-21 mm Hg <input type="checkbox"/> 20-30 mm Hg or 23-32 mm Hg <input type="checkbox"/> 30-40 mm Hg or 34-46 mm Hg
<input type="checkbox"/> Glove, class:	<input type="checkbox"/> 15-20 mm Hg or 15-21 mm Hg <input type="checkbox"/> 20-30 mm Hg or 23-32 mm Hg
<input type="checkbox"/> Velcro device	
<input type="checkbox"/> Compression garment for nighttime use	
<input type="checkbox"/> Breast swell spot (if breast involvement)	
<input type="checkbox"/> Donning and doffing instruments	
Renew x 12	
<b>Diagnosis: Right, left, or bilateral lower limb lymphedema</b>	
<input type="checkbox"/> Multi-layer bandage kit for reduction therapy for right, left, or bilateral limb(s)	
<input type="checkbox"/> Compression garment(s) for daytime use:	
<input type="checkbox"/> Knee high, class:	<input type="checkbox"/> 15-20 mm Hg or 18-21 mm Hg <input type="checkbox"/> 20-30 mm Hg or 23-32 mm Hg <input type="checkbox"/> 30-40 mm Hg or 34-46 mm Hg
<input type="checkbox"/> Thigh high, class:	<input type="checkbox"/> 15-20 mm Hg or 18-21 mm Hg <input type="checkbox"/> 20-30 mm Hg or 23-32 mm Hg
<input type="checkbox"/> Compression garment for nighttime use	
<input type="checkbox"/> Genital swell spot (if genital involvement)	
<input type="checkbox"/> Donning and doffing instruments	
Renew x 12	
<b>Diagnosis: head and neck lymphedema</b>	
<input type="checkbox"/> Head and neck compression garment	
Renew x 12	





# Kompresyon Tedavisi Kontrendikasyonları:

- Arteriyel yetmezlik
- Şiddetli periferik arteriyel tıkaçıcı hastalık
- Akut selülit
- Kontrolsüz kalp yetmezliği
- Akut dermatit
- Duyu kaybıyla birlikte şiddetli diyabetik nöropati veya cilt nekrozu riski taşıyan mikroanjyopati
- Kompresyon malzemesine karşı gerçek alerji



## **MASAJ:**

- Lenfödem tedavisinde geniş olarak kullanılmakta
- Amaç lenfatik damarları aktive ederek drenajı arttırmak
- Hasta tarafından yapılan retrograt veya uzman tarafından kompleks masajı
- Masaj ile ödem azalması sağlandıktan sonra kompresyon bandajları ile etki korunur



# Farmakolojik Tedaviler:

**Diüretikler:** lenfödem gibi yüksek protein içeren ödemlerde etkisi yok. Başlangıçta su atımı ile ödemi azaltır ancak basınç farkı aynı kalır, uzun dönemde osmotik basıncı arttırarak zararlı olur.

**Benzopyrone:** Lenfödem olan kolda protein depozit yıkımını arttırarak interstisyel onkotik basıncı düşürmesi beklenmektedir. Ancak bilimsel olarak placeboya üstünlüğü saptanmamıştır ve %6 hepatotoksite saptanmıştır.



## **Anti-inflammatory Agents**

- Non-steroidal Anti-inflammatory Drugs (NSAID)
- Tetrasiklinler
- Neutralizing Antibodies
- Tacrolimus

## **Anti-fibrotic Therapies**

Topical application of pirfenidone (PFD)

# Farmakolojik tedavi klinik çalışmaları:

Trial	Agent	Phase	N	Design	Primary outcome	Results
NCT02257970 [136]	Ketoprofen	4	89	Open label exploratory, then randomized, double-blind, placebo-controlled trial of pts with arm or leg LE	Exploratory Phase: Derm. score Randomized Phase: Skin thickness	Exploratory Phase: Score improvement – 3.4 ( $p < 0.0001$ ) Randomized Phase: Skin thickness reduced ( $P = 0.01$ ), but no change in limb volume
NCT04243837 [137]	LYT-100	1/2	100	Part 1: Dose escalation Part 2: Food effect study Part 3: Randomized, double-blind, placebo-controlled trial in pts with Stage 1 or 2 BCRL	Part 1: safety, MTD Part 2: PK, food effect Part 3: Efficacy signals	Part 1: well tolerated, MTD not reached at 100–1000 mg BID Part 2: 19% lower exposure in fed vs. fasting Part 3: Results not yet reported
NCT02994771 [138]	Lymfactin®	1	15	Single-arm trial of adenoviral VEGF-C combined with VLNT in pts with BCRL	Safety	Well tolerated, no DLT at maximum dose
NCT03658967 [139]	Lymfactin®	2	39	Double-blind, randomized, placebo-controlled trial of adenoviral VEGF-C combined with VLNT in pts with BCRL	Arm volume; Lymphatic flow by lymphoscintigraphy; QoL per LQOLI	Company press release states that results were "inconclusive" [140]
NCT04390685	Tacrolimus, topical	1/2	60	Single-arm study of tacrolimus ointment following ALND for BCRL prevention	Arm volume change by water displacement	Not yet reported
NCT04541290	Tacrolimus, topical	1/2	20	Single-arm study of tacrolimus ointment in pts with existing BCRL	Arm volume change by water displacement	Not yet reported
NCT02494206 [141]	QBX258	NS	9	Single-arm study of anti-IL4/ anti-IL13 blockade in Stage 1 or 2 BCRL	Arm volume change by perometry	Arm volume significantly increased relative to baseline ( $P = 0.046$ )

ALND axillary lymph node dissection, BCRL breast cancer-related lymphedema, BID twice-daily, LE lymphedema, LQOLI lymphedema quality of life inventory, MTD maximum tolerated dose, NS not specified, QoL quality of life, VEGF-C vascular endothelial growth factor C, VLNT vascularized lymph node transfer

## Current Breast Cancer Reports

**Table 1** Pharmacological interventions for the treatment of lymphedema

Type of intervention	Proposed mechanism for lymphedema treatment	Authors, publication year
<b>Systemic interventions</b>		
<b>VEGF-C</b>	<i>Lymphangiogenesis</i>	Szuba et al., 2002
Subcutaneous injection	VEGF-C directly binds VEGFR-3 to activate intracellular signaling pathways that promote LEC growth and survival	
<b>VEGF-C</b>	<i>Lymphangiogenesis</i>	Yoon et al., 2003
Naked plasmid technique	Transfer of plasmid DNA encoding VEGF-C increases VEGFR-3 expression and activation	
<b>VEGF-C</b>	<i>Lymphangiogenesis</i>	Lai et al., 2002
Viral vectors:	Adenoviral and adeno-associated gene vectors encoding VEGF-C regenerate lymphatic vessels and preserve lymphatic architecture post VLNT	Tammela et al., 2007
— Adenovirus		Hartiala et al., 2020
— Lymfactivin®		
Adeno-A associated		
<b>VEGF-C</b>	<i>Lymphangiogenesis</i>	Pardi et al., 2018
mRNA vectors	Nucleoside-modified mRNA encoding VEGF-C stimulates site-specific lymphatic growth at low dosages	Brown et al., 2020
		Sziöke et al., 2021
Hepatocyte growth factor (HGF)	<i>Lymphangiogenesis</i>	Kajjya et al., 2005
	VEGFR-3 independent stimulation of LEC proliferation and migration	Wong et al., 2021
9-cis retinoic acid (RA)	<i>Lymphangiogenesis</i>	Choi et al., 2012
	Indirect activation of PI3K/Akt pathway via fibroblast receptor signaling to stimulate LEC proliferation	Wong et al., 2021
Adipose-derived stem cells (ADSCs)	<i>Lymphangiogenesis</i>	Hwang et al., 2011
	ADSCs release a secretome of bioactive factors that reinforce LEC growth and survival	Ahmadzadeh et al., 2020
		Yan et al., 2011
Ketoprofen (NSAID)	<i>Anti-inflammatory</i>	Nakamura et al., 2009
	5-Lipoxygenase (5-LO) inhibition,	Tian et al., 2017
	↓ leukotriene B4 (LTB4) synthesis	Rockson et al., 2018
Bestatin (NSAID)	<i>Anti-inflammatory</i>	Tian et al., 2017
	Leukotriene A4-hydrolyase (LTA4H) inhibition,	Cribb et al., 2021
	↓ leukotriene B4 (LTB4) synthesis	
Fingolimod (Gilenya®)	<i>Anti-inflammatory</i>	García Norez et al., 2018
	Inhibition of activated CD4+T cell emigration from LNIs impairs TH2 differentiation	
Neutralizing antibodies	<i>Anti-inflammatory</i>	Avnham et al., 2013
	Th2 inflammatory cytokine blockade (IL-4/IL-13 inhibition)	Savetsky et al., 2015
		Mehrams et al., 2021
Doxycycline	<i>Anti-inflammatory</i>	Debrah et al., 2006
	Inhibition of Th2 phenotype differentiation,	Mand et al., 2012
	↓ monocyte recruitment,	Furion-Silva et al., 2021
	↓ polarization of alternatively activated M φ	Brown et al., 2023
Anti-transforming growth factor beta-1 (TGF-β1)	<i>Anti-fibrotic</i>	Meng et al., 2016
	Inhibition of TGF-β1 disrupts fibroblast maturation to myofibroblasts, improving lymphostatic fibrosis	Yoon et al., 2020
<b>Topical interventions</b>		
hADSCs and VEGF-C hydrogel	<i>Lymphangiogenesis</i>	Hwang et al., 2011
	hADSC mediated sustained release of VEGF-C	
Recombinant human fibroblast growth factor 2 (FGF2)	<i>Lymphangiogenesis</i>	Onishi et al., 2014
	↑ VEGF-C and VEGF-D expression	
Tacrolimus	<i>Anti-inflammatory</i>	Gardenier et al., 2017
	Inhibition of IL-2-mediated CD4+T cell activation/differentiation	Gulmark Hansen et al., 2023
Pirfenidone	<i>Anti-fibrotic</i>	Baik et al., 2022
	Inhibition of TGF-β1	
Captopril	<i>Anti-fibrotic</i>	Brown et al., 2023
	ACE inhibitor— inhibition of intracellular TGF-β1 signaling pathways	

Abbreviations: VEGF vascular endothelial growth factor, VEGFR vascular endothelial growth factor receptor, LEC lymphatic endothelial cell, DNA deoxyribonucleic acid, VLNT vascularized lymph node transplant, mRNA messenger ribonucleic acid, IL interleukin, hADSCs human adipose-derived stem cells



# Cerrahi tedavi:

Nadiren tüm konservatif tedaviler başarısız ise uygulanır.

İki tür cerrahi uygulanır:

- Reduktif
- Fizyolojik





## **Reduktif:**

Ekstremitenin fazla subkutan dokusu eksizyonu veya liposuction.

Altta yatan hastalık tdv edilmez.

Kötü iyileşme, enfeksiyon ve rekürrens görülebilir.

## **Fizyolojik:**

Lenfatik sıvı drenajını arttırmaya yöneliktir.

Lenfatik kanalların rekonstrüksiyonu

Lenfatik doku (omental flab) getirilmesi



## Photobiomodulation (PBM):

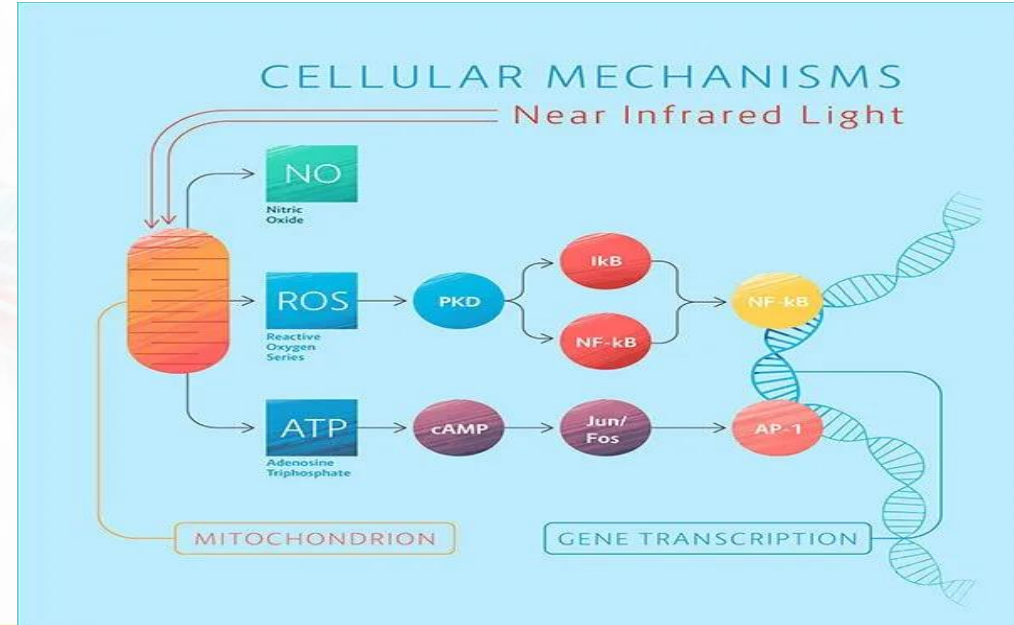
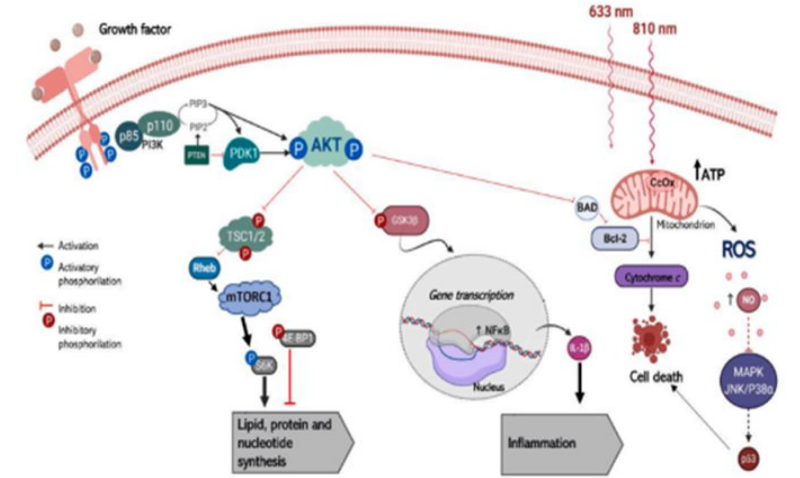
Düşük seviyeli lazer olarak da bilinen fotobiyomodülasyon (PBM) bir fototerapi türüdür.

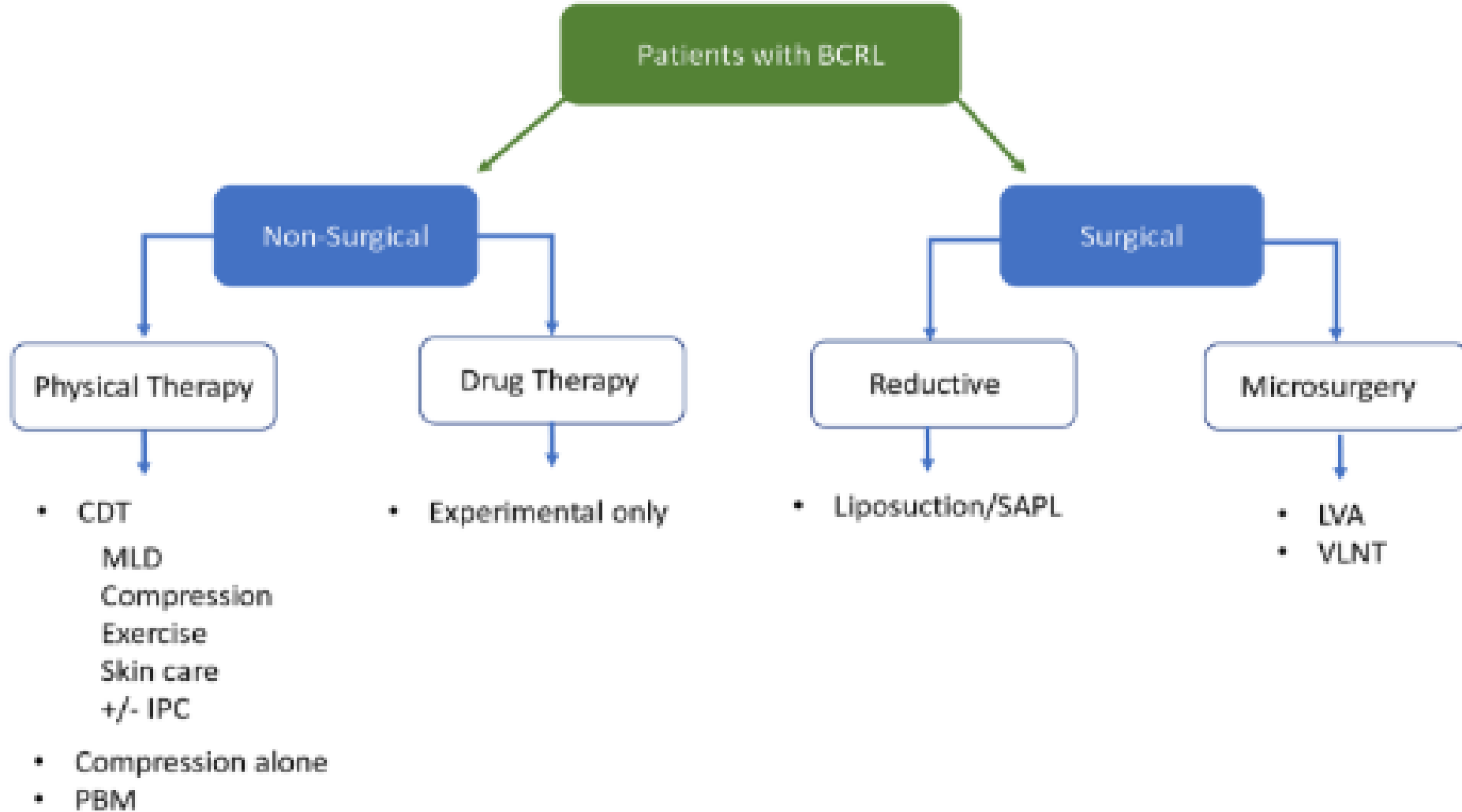
Hedef bölgeye 650 ila 1000 nm arasındaki dalga boyları düşük hızda teslim edilir.

PBM ; inflamasyonu azaltması , lenfatik hareketliliği sağlaması , rejenerasyon ve fibrozisin önlenmesi gibi etkileri olduğu literatür çalışmalarında gösterilmiş.

M.C.P. Felician et al.

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# Sabrınız için teşekkür ederim..



## Hadrianus



İmparator Hadrianus'un heykeli, Münih

### 14. Roma İmparatoru

Hüküm süresi	10 Ağustos 117 - 10 Temmuz 138
Önce gelen	Trajan
Sonra gelen	Antoninus Pius
Doğum	24 Ocak 76 Italica, İspanya
Ölüm	10 Temmuz 138 (62 yaşında) Baiae