Morbidity associated with breast cancer therapy and the place of physiotherapy in its management

Rodica Păcurar[1], Codruţa Miclăuş[2], Marius Miclăuş[3]

Abstract

Incidence of breast cancer continues to grow while modern diagnosis and treatment techniques improve long-term survival rates of the patients. Hence, more women will experience morbidity associated to breast cancer treatment. The aim of this article is to provide a review of the morbidity associated with breast cancer treatment and to emphasize the role of physiotherapist within the rehabilitation team. Pain, pectoralis tightness and axillary web syndrome are the most frequently encountered surgical side effects. They contribute to upper arm dysfunction and reduced range of motion. Radiotherapy may lead to skin and pulmonary morbidity, lymphedema and dysfunction of the muscles caught in the radiation field. Chemotherapy and hormone therapy are associated with osteoporosis and weight gain, the latter representing an important risk factor to lymphedema. Secondary lymphedema is the most frequent complication of breast cancer treatment, mostly related to axillary surgery and radiotherapy. Physiotherapeutic techniques may prevent and control lymphedema, scar adherence and pulmonary complications, reduce pain and improve range of motion, which results in a better quality of life for the patients.

***Key words**: breast cancer, lymphedema, mastectomy, physiotherapy, radiotherapy.*

Rezumat

Incidența cancerului de sân continuă să crească în timp ce diagnosticul şi modalitățile moderne de tratament îmbunătățesc supraviețuirea pe termen lung a pacientelor. Astfel, patologia asociată tratamentului cancerului de sân va fi întâlnită la tot mai multe femei. Scopul acestui articol este acela de a oferi o recenzie a patologiei asociate cu tratamentul cancerului de sân şi de a sublinia rolul kinetoterapeutului în cadrul echipei de reabilitare. Cele mai frecvent întâlnite efecte secundare ale intervenției chirurgicale sunt durerea, contractura pectorală şi dezvoltarea de benzi fibrotice. Ele contribuie la disfuncția membrului superior şi la reducerea mobilității. Radioterapia poate duce la modificări cutanate şi pulmonare, limfedem şi disfunctii ale muşchilor din câmpul iradiat. Chimioterapia şi terapia hormonală sunt asociate cu osteoporoza şi creşterea în greutate, ultima reprezentând un important factor de risc pentru limfedem. Limfedemul secundar este cea mai frecventă complicație a tratamentului cancerului de sân, fiind asociat, in principal, cu chirurgia axilară şi radioterapia. Tehnicile kinetoterapeutice pot

[1] MD, PhD, Municipal Hospital of Timişoara, *e-mail: pacrodi@yahoo.com*
[2] MD, Assist. Lecturer PhD, Clinic of Surgical Oncology and Surgical Semiology, University of Medicine and Pharmacy "Victor Babeş"of Timişoara
[3] MD, Assist. Lecturer PhD, Second Surgical Clinic, University of Medicine and Pharmacy "Victor Babes" of Timişoara

preveni şi controla limfedemul, aderența cicatricială şi complicațiile pulmonare, pot reduce durerea şi creste mobilitatea, ceea ce va duce la o mai bună calitate a vieții pacientelor.

***Cuvinte cheie**: cancer de sân, kinetoterapie, limfedem, mastectomie, radioterapie.*

Introduction

Breast cancer is the most frequent cause of cancer death among females between 20 and 59 years old and its incidence continues to increase. Some of the reasons why this pathology is more often detected in present could be: i) increased mammographic screening, ii) growing use of oral contraceptives and hormone replacement therapy, and iii) increasing prevalence of obesity [1]. Modern imagistic techniques permit an early detection while advances in treatment options improve the long-term survival rates. The consequence for physiotherapists is that they will encounter more often in their work breast cancer survivors with their specific complications due to surgery and adjuvant therapy. The aim of this article is to review the morbidity associated with breast cancer therapy and to emphasize the role of physiotherapist as part of the team who manages these problems.

Immediate morbidity associated with surgical procedures

Radical mastectomy introduced by Halsted in 1894 was the most frequently procedure performed on women with breast cancer in the past. It consisted in removal of the entire breast, nipple/areolar region, the pectoral major and minor muscles and clearance of axillary nodes. This procedure is rarely used today and is associated with high incidence of upper limb lymphedema (ULL), reduced shoulder range of motion (ROM), pain, numbness and muscle weakness.

In 20th century, Patey and Dyson in 1940 and Madden in 1960 introduced modified radical mastectomy (MRM) with less damage to the patient. Patey MRM consists in removal the entire breast, nipple/areolar region, pectoralis minor, interpectoral and axillary lymph nodes. Madden MRM consists in removal of the entire breast, nipple/areolar region, pectoralis major's fascia, interpectoral and axillary lymph nodes, with preservation of both pectoralis muscles. MRM is the most widely used surgical procedure to treat operable breast cancer, presently. Although less aggressive, MGM still is associated with lymphedema and reduced shoulder ROM.

Recently, sentinel node biopsy has been introduced to predict lymph nodal status. When the sentinel node (the first draining lymph node) is negative for metastatic disease, axillary node dissection can be avoided and surgical procedure is limited to the breast area: a) quadrantectomy - removal of a quarter of the breast including the skin and breast fascia, b) partial or segmental mastectomy - removal of a portion of the breast tissue and a margin of normal breast tissue, c) lumpectomy - removal of the breast tumor and a surrounding margin of normal breast tissue or d) excisional biopsy.

Even with modern procedures, the breast cancer surgery may affect body posture, flexibility and strength of the upper limb. Sustained pectoralis tightness after breast cancer treatment pulls the scapula into a protracted and depressed position

leading to decreased upward rotation of the scapula which is likely to be implicated in impingement syndrome [2]. Moreover, after surgical intervention patients tend to protect their surgical area by thoracic flexion and scapula protraction. Typical protective posture consists in head tilted forward, shoulder raised and hunched, elbow bent so that the hand on affected part rests across the belly and body bends forward at the waist. In time, adverse changes in body posture may develop, consisting in asymmetry of trunk and shoulder girdle and greater forward leaning of the trunk. Regular rehabilitation keeps the angle of body inclination on the same level and improves trunk symmetry, position of scapulas and shoulder girdle [3]. Postoperative pain is a common symptom among breast cancer patients because of surgical trauma or muscular spasm in the cervical, upper thoracic and scapular region by muscular protection. Intercostobrachial nerve injury occurs in 80-100% of patients undergoing axillary dissection and is the major cause of axillary pain. Pain enhances pectoralis hypertonic through pain-induced contraction, scapular protraction aggravating shortening. In time, scapular retractors become overused and strained with increased risk to myofascial disfunction in the back and neck muscles. The physiotherapist can minimize the pain using massage therapy with relaxing effects.

Myofascial dysfunction is a regional pain syndrome characterized by presence of “trigger points”. They represent circumscribed spot tenderness in a nodule that is part of a palpably tense band of muscle fibers. These points respond to external pressure, stretch or muscle recruitment with radiating pain; weakness of the muscle is also present. Physical therapy consists in “myofascial release techniques”, daily stretching of symptomatic muscles and resistive activities addressed to strength deficits.

Axillary web syndrome is a condition following surgical removal of axillary lymph nodes during which patients may develop palpable “cords” or fibrotic bands originating in the axilla and extending distally along the anterior or medial surface of the arm, often below the elbow down to the palm. The cords are sclerosed veins and lymphatic vessels made redundant by surgical maneuvers in the axilla, surrounded by fibrosis area. Axillary webs develop between weeks 1 and 5 after axillary clearance, placing the patients at risk for reduction in shoulder ROM with altered movement patterns. Physical therapy consists in manual fibrous release techniques, gravity-assisted pendulum exercises for shoulder ROM, wall walking, active assisted forward flexion and passive end-ranging of internal and external rotation [2].

Frozen shoulder following surgical treatment is frequent in breast cancer patients, even after sentinel lymph node biopsy. Restricted abduction appears due to soft tissue contractures. Early shoulder remobilization with abduction and forward flexion, wall walking and pendulum exercises can prevent chronic functional limitation and restricted ROM associated to this complication [2].

Pulmonary morbidity among breast cancer patients may occur related to surgery, anesthetics and prolonged confinement to bed. During the surgery thoracic nerve may be injured causing the serratus anterior muscle to weaken. Furthermore, pain and discomfort from the surgical incision may restrict patient’s thoracic movements with decreased diaphragmatic movement, decreased pulmonary expansion and consequently restricted pulmonary function, pulmonary secretion accumulation or atelectasia. Postoperatory confinement to bed may increase the pulmonary dysfunction through muscle atrophy. Preoperatory respiratory muscular training provided by the physiotherapist not only improves

tissue oxygenation facilitating proper surgical conditions but also, prevents pulmonary morbidity if postoperatory continued.

Transient lymphostasis – an increase of less than two cm in circumferential difference between limbs – may occur on the affected side following surgery. Until normal lymph circulation is restored after surgery large molecules, proteins, and debris accumulate in the interstitium distal to the lymph node removal. Progressive accumulation can lower the threshold for nociceptive impulse transmition leading to pain, hypersensitivity and allodynia. Persistent pain may lead to abnormal muscle recruitment, restricted shoulder ROM and biomechanical malalignment. Treatment of lymphostasis is mainly the physiotherapist's task: manual lymphatic drainage, progressive ROM and deep breathing exercises.

Without a regular exercise programme, breast cancer treatment may result in upper extremity dysfunction. The main limited motions are flexion, abduction and external rotation at 90 degrees of arm abduction [1]. Early beginning of physiotherapy can improve shoulder ROM and functional capacity without causing adverse effect in postoperative period [4].

Immediate morbidity associated with adjuvant treatment

Radiotherapy, chemotherapy and hormone therapy are adjuvant means used to cure and to prevent relapse in breast cancer patients.

Radiotherapy is recommended to all patients receiving conservative surgery and to those at risk of recurrence. It consists in 5 weekly sessions for up to 6 weeks. Radiotherapeutic fields usually involve the breast and chest wall, the supraclavicular fossa and, sometimes, the axilla. Besides the effect on neoplastic cells, high energy X-rays produce local damage to healthy tissue. Injury of the local vessels affects the muscle nutrition while alteration of the parenchyma including connective tissue limits the muscle expanding during contraction. The result consists in muscle ischemia and inefficient contraction together with subcutaneous fibrosis with the fixation to the lower musculature which leads to movement limitation. The muscles caught in radiation field are pectoralis major, serratus anterior and latissimus dorsi. Direct effects of the X-rays on irradiated tissue consists in increased sensitivity and desquamation together with inflammation. All these changes promote pain and pain-protective behaviours which, in time, result in contractures, limited ROM and arm weakness.

Radiation pneumonitis (RP) may occur from 1 to 6 months after radiotherapy manifesting by dyspnea, cough, fever and altered pulmonary function tests. Early physiotherapy during irradiation minimizes respiratory complications. The role of the physiotherapist during radiotherapy in breast cancer patients is to provide a programme which includes pectoral muscle stretching, shoulder ROM and aerobic exercises.

Transient lymphostasis during radiotherapy may, also, appear.

Chemotherapy associates with a significantly greater risk for osteoporosis. Among women who have had chemotherapy, bone loss may occur much sooner than it normally might. Moreover, chemotherapy may prompt an early, sometimes permanent menopause followed by sarcopenia with changes in body muscle/fat ratio. Accumulating body fat places postmenopausal women at risk for relapse. More than 70% of breast cancers are promoted by

estrogens and higher estradiol concentrations significantly predict cancer recurrence [5].

Aromatase, an enzyme responsible for a key step in the biosynthesis of estrogens from androgens, is found in many tissues, primarily in adipose tissue in postmenopausal women. More adipose tissue equals more aromatase and more circulating estrogen. Additionally, bioavailability of estradiol depends on the blood level of sex hormone-binding globulin (SHBG). Circulating estradiol is bound mostly to SHBG. Only a small fraction is "free" and thus biologically active and able to activate its receptor on cancer cells. Overweight women have higher amounts of insulin and insulin-like growth factor 1 which decrease SHBG, making more estrogen bioavailable.

Aromatase inhibitors are drugs used in the management of patients with breast cancer whose malign cells were found to be estrogen receptor positive. Postmenopausal women who use aromatase inhibitors are also, at risk to bone loss. During the first year after diagnosis, women tend to be less physically active. Reasons include fatigue associated with radiotherapy, side effects of chemotherapy and loss of energy spent for recovery. Taking these reasons into consideration, it seems reasonably to fight against osteoporosis and to combat or prevent overweight in women who undergo anticancer medication. Besides nutrition counseling, a physical training program is warranted. The physiotherapist may provide aerobic exercises, cardiovascular training or light-weight strength-training in order to maintain or lose weight, as necessary [6] .A particular period of time is represented by chemotherapy when its side effects – nausea, vomiting, increased risk of infections due to neutropenia – hinder women to attend physical training courses. Home exercises during chemotherapy are an alternative and the physiotherapist should provide a comprehensive written home-based training programme.

Long-term morbidity associated with breast cancer treatment

The main long-term pulmonary complication following radiotherapy is pulmonary fibrosis (PF). It develops in time, usually manifests after 6 months from radiotherapy completion and persists throughout the patient's life. Among respiratory exercises, the physiotherapist may use a scapular waist musculature lengthening programme, pulmonary re-expansion manual maneuvers, bronchial hygiene exercise guidance and incentive spirometry.

Radiation induced fibrosis (RIF) is a consequence of the damage to normal tissues caused by high-dose radiotherapy. Usually, RIF stabilizes 2 years after radiotherapy and skin retraction, atrophy and toughness to palpation and decreased tissue compliance are associated. Palpation and using a tissue compliance meter are methods of measuring tissue compliance [7]. The fibrosis is initially caused by elevated deposition of collagen and is maintained or aggravated by impairment in vascularization. Studies report that about 45% of patients experience frequent to constant breast pain associated with RIF which provokes patient's anti-pain attitudes, limited ROM and diminished quality of life. Pain-release techniques could be useful on this stage. A pilot study conducted by Lennox et al, demonstrated the effectiveness of impedance-controlled microcurrent therapy in remediation of ROM limitations associated with RIF [8].

In addition, axillary radiation is considered a prognostic factor for the development of shoulder morbidity. A cross sectional study comprising 74 women with the time since surgery varying from 6

months to 6 years found decreased EMG activity of upper trapezius, rhomboid and pectoralis major and small pectoralis major and minor using MRI scans. Loss of muscle activity was enhanced on the downward movement, at the highest point of elevation and the longer the time since surgery. Shoulder Pain and disability Index analysis found diminished ability to carry out ADL tasks, reduced health-related quality of life and psychosocial distress associated to pain after treatment for breast cancer [9]. A case-control study conducted by Harrington S et al, compared 24 breast cancer survivors who completed their treatment (surgery, chemotherapy and/or radiotherapy) no greater than 6 months and a control group of healthy, age and gender match participants. They found significant differences for active flexion, extension, passive flexion and external rotation at 90 degrees; also, significant differences were found concerning the strength measures between groups for abduction and upward rotation, depression and adduction, flexion, external rotation, internal rotation, scaption and adduction [10].

Post-mastectomy pain syndrome (PMPS) consists in pain persisting beyond the period of normal healing after mastectomy, lumpectomy and/or axillary surgery. It is considered to be a neuropathic pain and several mechanisms by which it appears have been proposed: intercostals brachial nerve damage, intra-operative compromise of cutaneous innervating, neuroma formation, fibrotic entrapment. Pain characteristics described by patients are numbness, tingling, pins and needles, burning or stabbing, on the same side as the surgery on chest wall, axilla or on the ipsilateral arm. Avoidance behaviors can develop leading in time to postural and mobility problems, including difficulties in performing activities of daily life (ADL). Some post-operative factors could aggravate PMPS: doing heavy house work, lying on the operated side, fibrosis after radiation on the brachial plexus or chemotherapy. Intervention consists in analgesics and physical therapy performed by a physiotherapist trained in pain management. Desensitization techniques, massage therapy, transcutaneous electrical nerve stimulation, topical cold or acupuncture should be included.

The most common complication related to breast cancer treatment is secondary lymphedema (LE). It is a consequence of axillary lymph node and vessels removal or damage during surgery and/or radiotherapy. LE consists in an abnormal edema, accumulation of tissue proteins and chronic inflammation localized mainly to the ipsilateral upper limb, but to the trunk, axilla or breast, either. Reported LE prevalence varies greatly among research teams due to the variations in definitions or measurements. Traditional measurements for LE include water displacement, circumferential measurements, calculation of volume, and bioelectric impedance [11]. In a survey among professionals specializing in lymphedema care, circumferential measurement was the primary method for diagnosis and monitoring of LE [12]. The precise mechanism of LE related to breast cancer therapy is debated because most of the cases do not appear as an immediate complication of the surgery, but in time, mostly within the first 3 years after surgery and radiotherapy; moreover, some patients do not develop LE at all while others experience this morbidity after many years from breast cancer treatment, even this didn't include axillary dissection or postoperative radiotherapy [13]. A 5-year, population-based prospective study conducted by Norman SA et al, found an incidence of 42% for lymphedema. Among the affected

women, lymphedema first occurred within 2 years of diagnosis in 80% and within 3 years in 89%. 61.2% of person-months of lymphedema involved the hand, 54.5% involved the lower arm, and 72.1% involved the upper arm [14]. Patients with LE are exposed to discomfort or pain, limited ROM, recurrent infections, non-healing wounds, difficulty with daily tasks, emotional and social distress. Without a proper management LE may lead to elephantiasis, paralysis of the limb, and lymphosarcoma. Once appeared, LE is incurable but the swelling can be controlled when LE is properly and early diagnosed and treated. Obesity and weight gain are known risk factors for the development of LE while slim body build and low values of the Quetelet, Rohrer and Pignet – Verwaeck indexes appear to be a factor protecting from the occurrence of lymphedema of the upper limb in women with radical breast amputation [15]. The treatment of lymphedema is difficult, time consuming and costly. Complete decongestive therapy (CDT) is considered to be the "gold standard" for LE treatment [16]. CDT consists in two phases: an initial reductive phase and a second, maintenance phase. Components of CDT are: (i) manual lymph drainage, (ii) multi-layer, short-stretch compression bandaging, (iii) lymphatic exercise, (iv) skin care and (v) education in lymphedema self-management, and elastic compression garments. In some patients, intermittent pneumatic compression therapy with multiple chambers pumps can be useful. A recent study proved the long-term benefit of low-level laser in the treatment of postmastectomy LE [17].

A systematic review and meta-analysis upon the benefits of conservative and dietary interventions for cancer-related lymphedema obtained the following results: level 1 evidence (strong evidence): for breast cancer patients with upper extremity lymphedema (UELE), whereas exercise was not found to improve or exacerbate existing UELE volume, significant benefit was found for LE symptoms of pain/tenderness and quality of life; level 2 evidence (moderate evidence): one high quality study demonstrated that caloric reduction for weight loss resulted in a 44% reduction in UELE volume. Moreover, observational data have shown a protective association between increased physical activity after breast cancer diagnosis and recurrence, cancer-related mortality, and overall mortality [18].

Impediments in physical rehabilitation of breast cancer patients

Physical rehabilitation of a patient after cancer treatment has to be part of an interdisciplinary approach. In order to obtain patient's adherence to the rehabilitative plan, the physiotherapist should be sustained by the other members of the rehabilitation team, especially by the surgeon and the oncologist. Despite of the growing evidence in the last years which support the benefits of rehabilitative interventions, there are still skeptic clinicians concerning the efficacy of physiatry to their patients. The absence of double-blind, randomized, placebo controlled trials represents a major barrier for the rehabilitation medicine to be accepted by medical doctors and surgeons [2]. Among some of them physical training continues to be believed to increase the risk of developing arm LE and therefore women with breast cancer are told to be careful or even to avoid such activities. Consequently, some patients may receive conflicting information regarding the need to attend a rehabilitation programme.

This lack of reliability together with the chronic financial problems of the sanitary system result in the absence, in Timisoara, of permanent physiotherapist posts in the surgical oncology or radiotherapy departments. Patients are provided

with little information by surgeons, radiotherapists and oncologists or nurses.

Patients' education and their financial status may add barriers in the efficacy of a rehabilitation programme. Physiotherapy sessions have to be completed by home-based exercise programmes. Adherence rates can be low, especially among patients without premorbid history of regular exercise [2]. Attending a private rehabilitation center or buying rehabilitation supplies such as bandaging materials for lymphedema may be an expensive exercise. Therefore, as long as regular structured physical activity is not integrated in cancer care and is not specifically recommended by doctors, most patients will continue to ignore it.

Conclusions

Morbidity associated to breast cancer treatment is complex and has long-terms manifestations. As part of the rehabilitation team, physiotherapist has a main task to promote adequate functional recovery and to prevent treatment complications. By specific techniques, the physiotherapist should maintain or restore proper body posture, range of motion, muscular strength, may prevent pulmonary complication, reduce pain and scar adherence. He has an essential role in controlling lymphedema of the upper limb. Recent strong-evidence data challenge the conception which hampers breast cancer survivors from physical training. To patients' benefit better co-operation between physiotherapists and doctors is expected to develop.

References

1. Gomide L.B., Matheus J.P.C., Candido dos Reis F.J. (2007) *Morbidity after breast cancer treatment and physiotherapeutic performance.* Int J Clin Pract 61, 972-982;
2. Cheville A.L., Tchou J. (2007) *Barriers to Rehabilitation Following Surgery for Primary Breast Cancer.* J Surg Oncol 95:409-418;
3. Rostkowska E., Bak M., Samborski W. (2006) *Body posture in women after mastectomy and its changes as a result of rehabilitation.* Adv Med Sci 51, 287-297;
4. Cinar N., Seckin U., Keskin D., Bodur H., Bozkurt B., Cengiz O. (2008) *The effectiveness of early rehabilitation in patients with modified radical mastectomy.* Cancer Nurs 31, 160-165;
5. Rock C.L., Flatt S.W., Laughlin G.A., Gold E.B., Thomson C.A., Natarajan L. et al (2008) *Reproductive Steroid Hormoones and Recurrence-Free Survival in Women with a History of Breast Cancer*. Cancer Epidemiol Biomarkers Prev 17, 614-620;
6. Kaelin C.M., Coltrera F., Gardiner J., Prouty J. (2007) *Pounds, muscles, and bones* in *The Breast Cancer Survivor's Fitness Plan*, Ed Mc Graw-Hill, New York, 21-38;
7. Wernicke A.G., Rosenblatt R., Rasca M., Parhar P., Christos P.J., Fischer A., Parashar B., Nori D. (2009) *Quantitative Assessment of radiation-Induced Fibrosis of the Breast with Tissue Compliance Meter, Palpation, and Radiological Imaging: Preliminary Results.* Breast J 15, 583-592;
8. Lennox A.J., Shafer J.P., Hatcher M., Beil J., Funder S.J. (2002) *Pilot study of impedance-controlled microcurrent therapy for managing radiation-induced fibrosis in head-and-neck cancer patients.* Int J Radiation Oncolgy Biol Phys 54, 23-34;
9. Shamley D.R., Srinanaganathan R., Weatherall R., Oskrochi R., Watson M., Ostlere S., Sugden E. (2007) *Changes in shoulder muscle size and activity following treatment for breast cancer.* Breast Cancer Res Treat 106, 19-27;
10. Harrington S., Padua D., Battaglini J., Groff D. (2011) *Comparison of shoulder flexibility, strength, and function between breast cancer survivors and healthy participants.* J Cancer Surviv 5, 167-174;
11. Quirion E. (2010) *Recognizing and treating upper extremity lymphedema in postmastectomy/lumpectomy patients: A guide for primary care providers.* J Am Acad Nurse Pract 22, 450-459;

12. Langbecker D., Hayes S.C., Newman B., Janda M. (2008) *Treatment for upper-limb and lower-limb lymphedema by professionals specializing in lymphedema care.* Eur J Cancer Care 17, 557-564;
13. Deutsch M., Land S., Begovic M., Sharif S. (2008) *The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone.* Int J Radiat Oncol Biol Phys 70, 1020-1024;
14. Norman S.A., Localio R., Potashnik S.L., Simoes Torpey H.A., Kallan M.J., Weber A.L., Miller L.T., De Michele A., Solin L.J. (2009) *Lymphedema in Breast Cancer Survivors: Incidence, Degree, Time Course, Treatment, and Symptoms.* J Clin Oncol 27, 390-397;
15. Kopanski Z., Wojewoda T., Wojewoda A., Schlegel-Zawadzka M., Wozniacka R., Suder A., Kosciuk T. (2003) *Influence of Some Anthropometric Parameters on the Risk of Development of Distal Complications After Mastectomy Carried Out Because of Breast Carcinoma.* Am J Hum Biol 15, 433-439;
16. http://www.lymphnet.org/pdfDocs/nIntreatment.pdf;
17. Kozanoglu E., Basaran S., Paydas S., Sarpel T. (2009) *Efficacy of pneumatic compression and low-level laser therapy in the treatment of postmastectomy lymphedema: a randomized controlled trial.* Clin rehabil 23, 117-124;
18. Mc Neely M.L., Peddle C.J., Yurick J.L., Dayes I.S., Mackey J.R. (2011) *Conservative and Dietary Interventions for Cancer-Related Lymphedema. A systematic review and Meta-Analysis.* Cancer 117, 1136-1148.