

Lung neoplasms: rehabilitation

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EVIDENCE COLLECTION METHODOLOGY

Articles were reviewed from the databases of MedLine (PubMed) and other sources of research on an open-ended basis. The search strategy was based on structured questions in the P.I.C.O. format (from the initials for Patient, Intervention, Control, and Outcome).

The descriptors used were (WeSH terms):

QUESTION 1: Lung Neoplasms AND (Exercise Therapy OR Exercise OR Exercise Movement Techniques OR Resistance Training OR Muscle Stretching Exercises OR Breathing Exercises);

QUESTION 2: Lung Neoplasms AND Exercise OR Exercise Therapy AND Preoperative AND Pulmonary Complications;

QUESTION 3: Lung Neoplasms AND (Physical Therapy Modalities OR Exercise OR Exercise Therapy) AND (Dyspnea OR Breathing Disorders);

QUESTION 4: Lung Neoplasms AND (Physical Therapy Modalities OR (Exercise OR Exercise Therapy) AND Postoperative Period AND (Fatigue OR Cancer-Related Fatigue);

QUESTION 5: (Cognitive Therapy OR Psychoeducational Intervention) AND (Lung Neoplasms) AND (Quality of Life);

QUESTION 6: (Lung Neoplasms OR Lung Cancer) AND (Exercise OR Physical Fitness OR Exercise Therapy OR Physical Fitness OR Physical Activity) AND (Exertion OR Exercise Tolerance);

QUESTION 7: (Creatine Supplementation AND Neoplasm) OR (Creatine Supplementation AND Cancer) OR (HMB Supplementation AND Neoplasm) OR (HMB Supplementation AND Cancer);

QUESTION 8: ("Paullinia" OR Paullinia Cupana OR Guarana) AND ("Neoplasms"[Mesh] OR Cancer OR Fatigue);

These descriptors were used as correlations according to the proposed theme of the P.I.C.O. questions. After analyzing this material, articles relative to the questions were selected that yielded evidence on which to base the present guideline.

QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS:

- A:** Experimental or observational studies of high quality;
- B:** Experimental or observational studies of lesser quality;
- C:** Case studies (uncontrolled studies);
- D:** Opinion with no critical evaluation, based on consensus, physiological studies, or animal models.

OBJECTIVE:

To offer information on the rehabilitation treatment of patients with lung cancer.

PROCEDURES:

Therapeutic rehabilitation interventions for the main clinical manifestations that compromise the quality of life, functionality, and daily life activities of patients with pulmonary neoplasia in the biopsychosocial ambit.

CONFLICTS OF INTEREST:

The authors have no conflicts of interest to declare.

INTRODUCTION:

Lung cancer is one of the most common malignancies in Brazil and the world.^{1,2} In 2008 it was the most diagnosed cancer in the United States and also the main cause of oncological death among men.^{1,2}

By the time of the diagnosis, more than 50% of lung cancer patients have already metastasized.³

As for clinical manifestations, the most frequent are cough, dyspnea, hemoptysis, chest pains, and hoarseness. Coughing is generally present in 50-75% of the patients.³

Dyspnea is also already a common symptom at the time of the diagnosis, occurring in approximately 25% of the cases.³ It can arise from: obstruction of the extrinsic or intraluminal airways, obstructive pneumonitis or atelectasis, dissemination of the tumor, lymphangitis, embolisms of the tumor or pneumothorax, pleural effusion, or pericardial effusion with tamponade.

These and other clinical manifestations can compromise the functionality and quality of life, in addition to being associated with fatigue among this population.

Therefore, just like in other types of cancer and chronic diseases, there is a growing concern in the search for therapeutic options to reduce fatigue, to improve the clinical, physical, and psychological symptoms - thereby improving the quality of life.

Accordingly, rehabilitation interventions emphasizing supervised therapeutic exercise constitute the foundation for the adjuvant treatment of this demographic. The Supervised Exercise Program constitutes a therapeutic intervention recommended for many cancer patients, including those with lung cancer, which is promoting relevant scientific studies and broadening the knowledge on its effect on the different clinical manifestations.

The objective of this guideline is to evaluate the efficacy of the rehabilitation strategies for the clinical conditions that are most common and of the greatest impact on the clinical evolution of these patients.

THErapy SESSION

1. WHAT ARE THE EFFECTS OF PHYSICAL EXERCISE ON LUNG CANCER PATIENTS?

The twice a day supervised training of strength and mobility in the first five post-operative days after surgery for resection of pulmonary neoplasia, followed by daily exercises at home for twelve weeks, based on the guidance of a physiotherapist during admission (which consisted of walking at the patient's limit, treadmill work, and exercise bicycle work at 60-80% of maximum cardiac rate for 5-10 minutes, combined with strength training of lower members with an initial load of between 0.9 and 1.8 kg) improved the strength of the quadriceps ($p = 0.04$) in the first five days after surgery, but did not reduce the time in hospital, nor did it improve the quality of life ($p > 0.05$), nor the tolerance to exercise ($p = 0.89$)⁴ (A).

Home exercises, done daily in the post-operative period, have no positive impact on the patient's perception of health, but it improved his capacity to participate in the changes and, consequently, could have a positive effect on the lung cancer patient's perception of health⁵ (A).

Breathing exercises combined with 30 minutes per day of aerobic exercise training, at 50% of maximum cardiac rate, five days per week for four weeks in patients with chronic obstructive pulmonary disease, candidates for pulmonary resection for non-small cells, improved their exercise capacity ($p < 0.001$)⁶ (B).

A daily 90-minute program of supervised breathing exercises combined with exercise bicycle work, exercises of the upper and lower limbs at a moderate intensity, and walking for a period of seven weeks increased the physical function, but did not improve the lung capacity and quality of life in patients with chronic obstructive pulmonary disease and inoperable lung cancer⁷ (B).

Patients with various types of cancer improved fatigue after an aerobic training program combined with resistance exercises for the trunk and upper and lower members (with a training load of between 30 and 100% of maximum repetitions) at a minimum frequency of twice a week during the post treatment period with radiation therapy and chemotherapy^{8,9} (A), and also patients with prostate cancer during radiotherapy found benefits in their quality of life with a supervised aerobic exercise program combined with resistance training¹⁰ (A).

Supervised aerobic exercises with an intensity of 80% of maximum cardiac rate done daily for three weeks reduced the fatigue symptoms

in patients with various cancer diagnoses (lung, stomach, colon, rectal) after the surgical treatment¹¹ (B). The aerobic training also had beneficial effects on the quality of life among patients surviving with breast cancer¹² (A).

A program of resistance exercises improved the well-being in patients of several types of advanced cancer during radiation therapy,¹³ (A) and also improved the quality of life among patients with breast cancer during their oncological treatment (chemotherapy, radiation therapy, or surgery)¹⁴ (A).

Supervised flexibility training significantly improves the quality of life of cancer patients both young and middle-aged shortly after chemotherapy¹⁵ (A).

RECOMMENDATION

Although the few studies with lung cancer patients have not revealed any consistent results,⁴⁻⁷ we recommend these patients regularly spend at least 150 minutes per week (spread out over 5 days) in physical, aerobic, and resistance training, either combined or separately, and supervised at first. The few studies made with this population were not sufficient and well-enough designed for us to conclude that exercising does not help with the symptoms of the disease, with the fatigue, and with their quality of life. Our recommendation is based on the proven benefits of physical exercise on patients with various types of cancer and at various phases of their oncological treatment.

2. DOES PRE-OPERATIVE EXERCISE DIMINISH POST-OPERATIVE PULMONARY COMPLICATIONS IN LUNG CANCER PATIENTS?

The occurrence of post-operative complications diminished significantly from 16.7% to 3% when respiratory physiotherapy and aerobic exercises were intensively done in the week preceding tumor resection surgery of the lung when compared to regular respiratory physiotherapy ($p < 0.05$).¹⁶

Pre-operative physiotherapy and pulmonary rehabilitation benefitted patients scheduled to do pulmonary resection for neoplasia. Improved capacity and preservation of pulmonary function was observed after surgery, however there was no clear association with any reduction in the incidence of post-operative complications.¹⁷

RECOMMENDATION

Intensive aerobic exercises combined with respiratory physiotherapy can be recommended for healthy patients scheduled for resection surgery for pulmonary neoplasia, for such a program shows the capacity to improve lung capacity and perhaps reduce the risk of post-operative complications.

3. DOES PHYSICAL EXERCISE IMMEDIATELY AFTER SURGERY REDUCE DYSPNEA IN LUNG CANCER PATIENTS?

A personalized, supervised aerobic physical exercise program consisting of three weekly sessions on a cycloergometer on alternate days for 14 weeks, running at 60% of maximum cardiac rate for 15-20 minutes in the beginning, with increases in duration of 5 minutes each week according to the tolerance of the patient (evaluated by hemodynamic signals, O₂ saturation, and an increase in the maximum cardiac rate up to 70%) in patients recently submitted to lobectomy or pneumonectomy due to lung cancer is capable of reducing complaints of dyspnea (averages and standard deviations pre- and post-intervention: 17 ± 5 and 20 ± 5 ; $p = 0.007$) measured in

the evaluation of functional well-being in the scale of quality of life from FACT-L (Functional Assessment Of Cancer Therapy-Lung).¹⁸

A personalized walking program, instituted for lung cancer patients not scheduled for surgery or for post-operative patients, with intensity and frequency of the walks set to increase in accordance with the monitoring of dyspnea complaints, with the objective of completing a circuit of ten meters as many times as possible until the symptom of pre-exhaustion as measured by the Berg Scale, twice a week for seven weeks improved the complaints of dyspnea based on the EORTCQLQ-C30 Quality of Life scale (average score between 50 and 33), however demonstrating no superiority over the control group in the immediate post-operative, nor between the surgical and non-surgical groups, but suggesting a qualitative improvement in their general well-being associated with the perception of the impact of dyspnea on the physical capacity and in the reduction of the vicious circle of dyspnea/sedentariness. Those patients who avoided exercise out of fear of dyspnea adhered to the therapeutic proposal with a reduction in symptoms, even though with low power for statistical conclusions⁷ **(B)**.

RECOMMENDATION

Supervised moderately intense aerobic exercises can be recommended for patients immediately after resection surgery for pulmonary neoplasia, especially where there is no recommendation for subsequent adjuvant chemotherapy. The intervention is safe and promotes a qualitative improvement of the general respiratory discomfort from exercise and of the dyspnea.

4. DOES PHYSICAL EXERCISE IMMEDIATELY AFTER SURGERY DIMINISH FATIGUE AMONG LUNG CANCER PATIENTS?

A personalized, supervised aerobic physical exercise program consisting of three weekly sessions on a cycloergometer on alternate days for 14 weeks, running at 60% of maximum cardiac rate for 15 to 20 minutes in the beginning, with increases in duration of 5 minutes each week according to the tolerance of the patient (evaluated by hemodynamic signals, O₂ saturation, and an increase in the maximum cardiac rate up to 70%) in patients recently submitted to lobectomy or pneumonectomy due to lung cancer is capable of reducing the fatigue and leg discomfort as measured by the evaluation of fatigue (averages and standard deviations pre- and post-intervention: 19 ± 8 and 12 ± 8; $p = 0.03$) measured in the evaluation of functional well-being in the scale of quality of life from FACT-L (Functional Assessment of Cancer Therapy-Lung).¹⁸

RECOMMENDATION

Supervised moderately intense aerobic exercises can be recommended for patients immediately after resection surgery for pulmonary neoplasia, especially where there is no recommendation for subsequent adjuvant chemotherapy. The intervention is safe and promotes a qualitative improvement from the complaint of exercise fatigue.

5. WILL A PSYCHOEDUCATIONAL PROGRAM WITH COGNITIVE AND BEHAVIORAL THERAPY IMPROVE THE QUALITY OF LIFE OF LUNG CANCER PATIENTS?

A psychoeducational program based on the patients' training and adoption of adaptive behaviors to delay the worsening of symptoms

with the following components: preparatory information, discussion of the experience of the symptom, exploration of the meaning and manifestations associated with the symptoms, consultations on strategies for facing them, and training and practice in progressive muscle relaxation, done by patients with advanced lung cancer (stage 3 and 4) on palliative radiotherapy, and capable of reducing the symptoms of anxiety ($p = 0.001$), fatigue ($p = 0.002$), functional ability ($p = 0.001$), and symptom clusters ($p = 0.003$)¹⁹ **(A)**.

A psychoeducational intervention, done once a week for four weeks by nurses giving guidance on education and food and counseling before the end of life and subsequent monitoring until death, improves the quality of life ($p = 0.02$) and mood ($p = 0.03$), but does not improve the intensity of the symptoms ($p = 0.24$), nor reduce stays in the hospital or the Intensive Care Unit, nor aid in the search for emergency services, when compared with patients receiving customary oncological care²⁰ **(A)**.

Cognitive and behavioral therapies applied by nurses for four sessions (initial, and then after 10, 20, and 32 weeks) on breast cancer patients (38%), lung (35%), and others with solid tumors (colon, gynecological, lymph nodes, and uterus) can improve the functionality, but the effect of this improvement is reduced when more symptoms of depression are shown by patients ($p < 0.01$)²¹ **(B)**.

RECOMMENDATION

We recommend a psychoeducational program by a health professional, preferably a psychologist trained and experienced in caring for chronically ill patients, focusing on guiding adaptive daily life behaviors, seeking coping strategies, and using relaxation techniques for patients with lung cancer at any phase of the disease, but a more intensive program for patients in the more advanced stages and during specific treatments.

6. CAN A PHYSICAL CONDITIONING PROGRAM FOR LUNG CANCER PATIENTS IMPROVE THEIR TOLERANCE FOR EXERCISE?

A supervised interdisciplinary rehabilitation program of a maximum of 20 sessions at least 5 times a week, composed of aerobic work on an exercise bicycle for at least 30 minutes at a moderate intensity (60 to 80% of maximum load) increased the tolerance to physical exercise on the 6-minute walking test with an average increase of 95.6 meters when compared with a control group with no intervention ($p < 0.001$)²² **(A)**. The same type of daily physical training for eight weeks on an exercise bicycle and treadmill for 20 minutes of each activity with intensity ranging from 60 to 80% of maximum load and values from 4 to 6 on the Borg Scale, in addition to motor physiotherapy to maintain range of movement and anaerobic strength activity of 3 to 15 repetitions with a load between 30 and 60% of one maximum repetition (1-RM) leads to an improvement in the 6-minute walking test: patients were able to walk 43.2% farther ($p = 0.002$)²³ **(B)**.

A supervised program of exercises immediately after surgery, twice a day, and continued as a home activity also twice a day, supervised at least once a month for 12 weeks, with motor activities for maintaining range of movement, strength training, gait, and free activity on a stationary bicycle, for 5 to 10 minutes, each modality, and of moderate intensity ranging from 60 to 80% of maximum cardiac rate did not improve the tolerance to exercise in the 6-minute walking test ($p = 0.47$)⁴ **(A)**.

RECOMMENDATION

Supervised interdisciplinary programs with aerobic training at a moderate intensity (60 to 80% of maximum load) for at least 30 minutes per session three times per week can be recommended for there is evidence of an improvement in tolerance to exercise, even if the physical activity is done on a cycloergometer or a stationary bicycle.

7. DOES ERGOGENIC SUPPLEMENTATION (B-HYDROXY-B-METHYL-BUTYRATE (HMB) + CREATINE) COMBINED WITH PHYSICAL EXERCISE REDUCE FATIGUE IN LUNG CANCER PATIENTS?

Creatine supplements with an initial dose of 5 g 4x/day for one week, followed by 7 weeks of 2.5 g 2x/day improved the bioimpedance and the ratio of extracellular mass/body mass ($p = 0.43$). This effect is greater in patients without a metastatic disease and who receive only fluorouracil/folic acid as chemotherapy. Patients with tumors in advanced stages or who are receiving more aggressive chemotherapy containing oxaplatin or irinocetan do not have the benefit of creatine supplements²⁴ (A).

Patients with wasting syndrome due to various types of advanced solid tumors (Stage III and IV) or with metastatic disease with weight loss between 2 and 10% did not improve their weight after supplementation with nutritional compound L-arginine (14 g/day), glutamine (14 g/day), and beta-hydroxy-beta-methylbutyrate (3 g/day) for 8 weeks ($p = 0.08$)²⁵ (B).

Patients with various types of advanced solid tumors (Stage IV) with weight loss > 5% and in different courses of treatment did not improve their weight by increased lean mass after supplementation with nutritional compound L-arginine (14 g/day), glutamine (14 g/day), and beta-hydroxy-beta-methylbutyrate (3 g/day) for 24 weeks ($p = 0.25$)²⁶ (B).

RECOMMENDATION

It is not possible to recommend the use of these supplements to reduce fatigue among patients with lung cancer for lack of evidence in the literature for this specific population. Meanwhile, as shown above, there is evidence of improvement in some parameters of bioimpedance among patients with colo-rectal neoplasia and an improvement of these parameters has been shown related to better survival and prognostic predictors in this population, and this must be taken into consideration in the decision to use these supplements. More studies are necessary to evaluate the effect of using ergogenics such as creatine and B-hydroxy-B-methylbutyrate (HMB) to reduce fatigue among cancer patients.

8. DOES GUARANA ("PAULLINIA CUPANA") REDUCE FATIGUE AMONG LUNG CANCER PATIENTS?

The extract of guarana (*Paullinia cupana*) at a dose of 50 mg twice a day for a period of 21 days can improve fatigue in breast cancer patients during chemotherapy when compared with a placebo ($p < 0.01$), does not produce any adverse effects or major toxicities, does not degrade the quality of sleep, nor does it cause anxiety or depression in this population²⁷ (B).

RECOMMENDATION

The extract of guarana at a dose of 50 mg twice a day can reduce fatigue in lung cancer patients, but the study demonstrating the

benefit was done with breast cancer patients. However, we must use caution, especially in patients with cardiopathy, essential arterial hypertension, and the elderly until more studies can show a safe dose regarding adverse effects, such as increased arterial blood pressure and cardiac rate.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893-917. DOI: <http://dx.doi.org/10.1002/ijc.25516>
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90. DOI: <http://dx.doi.org/10.3322/caac.20107>
3. Chute CG, Greenberg ER, Baron J, Korson R, Baker J, Yates J. Presenting conditions of 1539 population-based lung cancer patients by cell type and stage in New Hampshire and Vermont. *Cancer*. 1985;56(8):2107-11.
4. Arbane G, Tropman D, Jackson D, Garrod R. Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. *Lung Cancer*. 2011;71(2):229-34 DOI: <http://dx.doi.org/10.1016/j.lungcan.2010.04.025>
5. Wall LM. Changes in hope and power in lung cancer patients who exercise. *Nurs Sci Q*. 2000;13(3):234-42. DOI: <http://dx.doi.org/10.1177/08943180022107627>
6. Bobbio A, Chetta A, Ampollini L, Primomo GL, Internullo E, Carbognani P, et al. Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2008;33(1):95-8. DOI: <http://dx.doi.org/10.1016/j.ejcts.2007.10.003>
7. Andersen AH, Vinther A, Poulsen LL, Mellemegaard A. Do patients with lung cancer benefit from physical exercise? *Acta Oncol*. 2011;50(2):307-13. DOI: <http://dx.doi.org/10.3109/0284186X.2010.529461>
8. Van Weert E, May AM, Korstjens I, Post WJ, van der Schans CP, van den Borne B, et al. Cancer-related fatigue and rehabilitation: a randomized controlled multicenter trial comparing physical training combined with cognitive-behavioral therapy with physical training only and with no intervention. *Phys Ther*. 2010;90(10):1413-25. DOI: <http://dx.doi.org/10.2522/ptj.20090212>
9. Adamsen L, Quist M, Andersen C, Møller T, Herrstedt J, Kronborg D, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. *BMJ*. 2009;339:b3410.
10. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*. 2009;27(3):344-51. DOI: <http://dx.doi.org/10.1200/JCO.2007.15.4963>
11. Dimeo FC, Thomas F, Raabe-Menssen C, Pröpfer F, Mathias M. Effect of aerobic exercise and relaxation training on fatigue and physical performance of cancer patients after surgery. A randomised controlled trial. *Support Care Cancer*. 2004;12(11):774-9. DOI: <http://dx.doi.org/10.1007/s00520-004-0676-4>
12. Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *J Clin Oncol*. 2003;21(9):1660-8. DOI: <http://dx.doi.org/10.1200/JCO.2003.04.093>
13. Chevillat AL, Girardi J, Clark MM, Rummans TA, Pittelkow T, Brown P, et al. Therapeutic exercise during outpatient radiation therapy for advanced cancer: Feasibility and impact on physical well-being. *Am J Phys Med Rehabil*. 2010;89(8):611-9. DOI: <http://dx.doi.org/10.1097/PHM.0b013e3181d3e782>
14. Haines TP, Sinnamon P, Wetzig NG, Lehman M, Walpole E, Pratt T, et al. Multimodal exercise improves quality of life of women being treated for breast cancer, but at what cost? Randomized trial with economic evaluation. *Breast Cancer Res Treat*. 2010;124(1):163-75. DOI: <http://dx.doi.org/10.1007/s10549-010-1126-2>
15. Thorsen L, Skovlund E, Strømme SB, Hornslien K, Dahl AA, Fosså SD. Effectiveness of physical activity on cardiorespiratory fitness and health-related quality of life in young and middle-aged cancer patients shortly after chemotherapy. *J Clin Oncol*. 2005;23(10):2378-88. DOI: <http://dx.doi.org/10.1200/JCO.2005.04.106>
16. Pehlivan E, Turna A, Gurses A, Gurses HN. The effects of preoperative short-term intense physical therapy in lung cancer patients: a randomized controlled trial. *Ann Thorac Cardiovasc Surg*. 2011;17(5):461-8. DOI: <http://dx.doi.org/10.5761/atcs.0a.11.01663>

17. Nagarajan K, Bennett A, Agostini P, Naidu B. Is preoperative physiotherapy/pulmonary rehabilitation beneficial in lung resection patients? *Interact Cardiovasc Thorac Surg.* 2011;13(3):300-2. DOI: <http://dx.doi.org/10.1510/icvts.2010.264507>
18. Jones LW, Eves ND, Peterson BL, Garst J, Crawford J, West MJ, et al. Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. *Cancer.* 2008;113(12):3430-9. DOI: <http://dx.doi.org/10.1002/cncr.23967>
19. Chan CW, Richardson A, Richardson J. Managing symptoms in patients with advanced lung cancer during radiotherapy: results of a psychoeducational randomized controlled trial. *J Pain Symptom Manage.* 2011;41(2):347-57. DOI: <http://dx.doi.org/10.1016/j.jpainsymman.2010.04.024>
20. Bakitas M, Lyons KD, Hegel MT, Balan S, Brokaw FC, Seville J, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *JAMA.* 2009;302(7):741-9. DOI: <http://dx.doi.org/10.1001/jama.2009.1198>
21. Doorenbos A, Given B, Given C, Verbitsky N. Physical functioning: effect of behavioral intervention for symptoms among individuals with cancer. *Nurs Res.* 2006;55(3):161-71. DOI: <http://dx.doi.org/10.1097/00006199-200605000-00002>
22. Cesario A, Ferri L, Galetta D, Pasqua F, Bonassi S, Clini E, et al. Post-operative respiratory rehabilitation after lung resection for non-small cell lung cancer. *Lung Cancer.* 2007;57(2):175-80. DOI: <http://dx.doi.org/10.1016/j.lungcan.2007.02.017>
23. Spruit MA, Janssen PP, Willemsen SC, Hochstenbag MM, Wouters EF. Exercise capacity before and after an 8-week multidisciplinary inpatient rehabilitation program in lung cancer patients: a pilot study. *Lung Cancer.* 2006;52(2):257-60. DOI: <http://dx.doi.org/10.1016/j.lungcan.2006.01.003>
24. Norman K, Stübler D, Baier P, Schütz T, Ocran K, Holm E, et al. Effects of creatine supplementation on nutritional status, muscle function and quality of life in patients with colorectal cancer—a double blind randomised controlled trial. *Clin Nutr.* 2006;25(4):596-605. DOI: <http://dx.doi.org/10.1016/j.clnu.2006.01.014>
25. Berk L, James J, Schwartz A, Hug E, Mahadevan A, Samuels M, et al. A randomized, double-blind, placebo-controlled trial of a beta-hydroxyl beta-methyl butyrate, glutamine, and arginine mixture for the treatment of cancer cachexia (RTOG 0122). *Support Care Cancer.* 2008;16(10):1179-88. DOI: <http://dx.doi.org/10.1007/s00520-008-0403-7>
26. May PE, Barber A, D'Olimpio JT, Hourihane A, Abumrad NN. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. *Am J Surg.* 2002;183(4):471-9. DOI: [http://dx.doi.org/10.1016/S0002-9610\(02\)00823-1](http://dx.doi.org/10.1016/S0002-9610(02)00823-1)
27. Oliveira Campos MP, Riechelmann R, Martins LC, Hassan BJ, Casa FB, Del Giglio A. Guarana (*Paullinia cupana*) improves fatigue in breast cancer patients undergoing systemic chemotherapy. *J Altern Complement Med.* 2011;17(6):505-12.