Immunonutritional Support in Lung Cancer Treatment

Akciğer Kanseri Tedavisinde İmmünonütrisyonel Beslenme Desteği

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ABSTRACT

Depending on the size of the tumour, metastasis status and the treatment method applied in lung cancer, the patient's appetite status and the use of nutrients in the body are adversely affected. Thus, the risk of developing conditions like malnutrition and sarcopenia increases. The response to treatment, quality of life and su rvival of the patient whose nutritional status is deteriorated are also adversely affected. In lung cancer patients, it is targeted to strengthen their immune system and antioxidant defence mechanisms and reduce inflammation with immunonutritional support. This review aimed to explain the role of glutamine, arginine, omega-3 fatty acids and RNA nucleotides, which are frequently used as immunonutritional support in medical nutrition treatment in lung cancer.

Key Words: lung neoplasms, nutrition support, glutamine, arginine, fatty acids, omega-3, inflammation

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ÖZET

Akciğer kanserinde tümörün boyutu, metastaz durumu ve uygulanan tedavi yöntemine göre hastanın iştah durumu, besinlerin vücutta kullanımları olumsuz etkilenmektedir. Bunun sonucunda da hastada malnütrisyon, sarkopeni vb. durumların gelişme riski artmaktadır. Beslenme durumu bozulan hastanın tedaviye yanıtı, yaşam kalitesi ve sağkalım durumu da olumsuz olarak etkilenmektedir. Akciğer kanseri hastalarında immünonütrisyonel beslenme desteği ile birlikte hastaların immün sisteminin ve antioksidan savunma mekanizmasının güçlendirilmesi, inflamasyonun azaltılması hedeflenmektedir. Bu derlemede immünonütrisyonel beslenme desteği olarak sık kullanılan glutamin, arjinin, omega 3 yağ asitleri ve RNA nükleotidlerinin akciğer kanserinde tıbbi beslenme tedavisindeki rolünün literatür bilgisi doğrultusunda açıklanması amaçlanmaktadır.

Anahtar Sözcükler: akciğer neoplazileri, beslenme desteği, glutamin, arjinin, omega-3 yağ asitleri, inflamasyon

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INTRODUCTION

According to the World Health Organization (WHO) Globocan 2020 data; lung cancer is the second most common type of cancer (11.4%) in the world among all cancer types, with 2.2 million new cases per year, but it is in the first rank (18%) among the causes of death from cancer. Although lung cancer is the most common type of cancer (14.3%) among men, it is in the third rank (8.4%) among women, following breast cancer (24.5%) and colorectal cancer (9.4%) (1). When examining the Globocan 2020 Turkey data, lung cancer constitutes 17.6% of new cancer cases in Turkey and ranks first. Lung cancer ranks first (25.8%) in new cancer cases among men; it is in fourth place (7%) among women, following breast cancer (23.9%), thyroid cancer (10.9%), and colorectal cancer (9.1%) (2). According to the mortality data originating from lung cancer in Turkey, cancer is the second leading cause of mortality after cardiovascular system diseases. Lung cancer has the highest mortality rate among cancer types (3).

Malnutrition, which occurs due to the impairment of digestion and nutrient absorption due to disease, decreased food intake, and increased nutritional need due to catabolism, is frequently seen in cancer patients. While severe malnutrition is seen in 50-80% of cancer patients, this condition reduces patients' survival and quality of life and delays the success of cancer treatment (4). There are many definitions of immunonutrition in the literature.

The definition of immunonutrition made by Grimble in 2001 was made as the intake of nutrients affecting the immune system, more than the amount met with normal daily nutrition. It has been shown that immunonutrition improves the clinical response by positively changing the inflammatory response to injury and infections (5). Nutritional support, which is started in the early period for oncology patients, positively affects the stress caused by inflammatory cytokines and effectively reduces tissue destruction by limiting the catabolic processes that may occur (6). Thus, in recent years, it has been aimed to support the patient's immune system with some particular nutrients rather than just meeting the energy and protein needs of the patient (7). It aims to strengthen the mucosal, cellular, and humoral immunity of the person and to fight local or systemic inflammation with the immunonutritional approach, which includes regulating the immune and inflammatory response (6, 7). It aims to improve the patients' clinical outcomes positively by improving the intestinal barrier function, supporting the antioxidant defence mechanism, controlling the inflammation that will occur in the body and supporting wound healing with immunonutritional nutrition (8). The most commonly used immune system supporting nutrients are glutamine, arginine, omega-3 fatty acids and RNA (ribonucleic acid) nucleotides (7).

This review aimed to explain the possible health benefits of the nutrients used in immunonutrition by biochemical means and to mention the role of immunonutritional support in medical nutrition therapy for lung cancer.

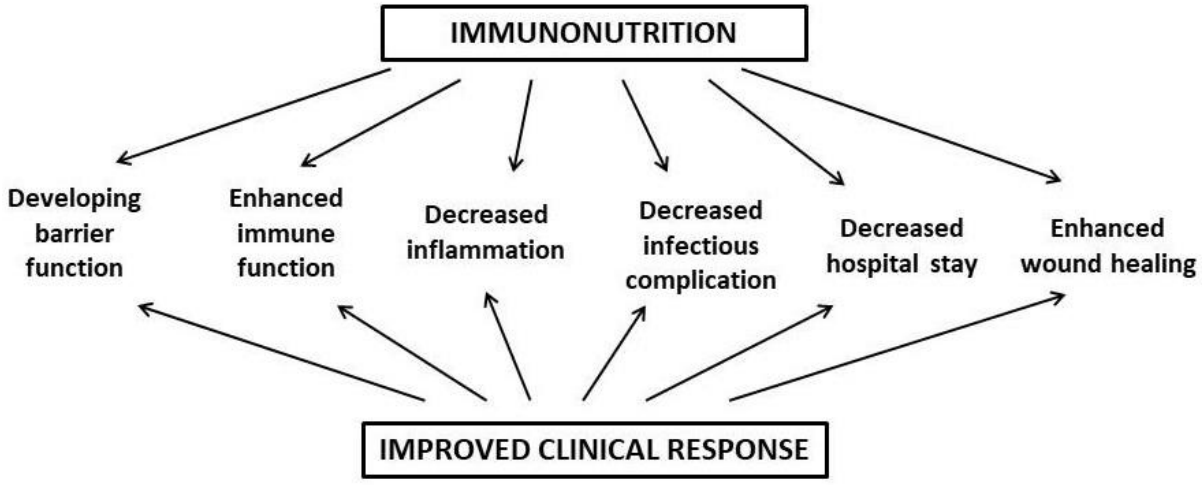

Figure 1. Immunonutrition in surgical and critically ill patients (Adapted from source number 8)

Possıble Health Effects of Immunonutrients

Glutamine

Glutamine is a neutral, semi-essential amino acid most abundant in the blood, constituting half of the free amino acid pool, and is very important for the intestinal mucosal structure (9). Since it plays a role in the synthesis of purine and pyrimidine bases, it is a precursor material in nucleic acid synthesis, amino acid synthesis and the production of glutathione, an important antioxidant. It is the body's primary energy source for the immune system, lymphatic system, and fibroblast cells. In some sources, it is stated that glutamine has a dual regulatory effect on the immune system. This double effect is explained as inhibiting the expression of inflammatory factors while simultaneously indicating a protective effect by supporting the immune system. (10). In animal experiments, it has been determined that glutamine improves T cell function and increases resistance to pathogen infections (8). Glutamine helps maintain intestinal functions as it is also an energy source for enterocytes (9, 11). It has been stated that glutamine modulates the inflammatory response in the intestine by decreasing IL-6 and IL-8 concentrations, and it also protects intestinal integrity by improving the intestinal-related immune tissue and cellular defence mechanism.

Glutamine deficiency causes morphological changes and bacterial translocation in the intestinal mucosa (8, 11). It is not essential as many body tissues can synthesise glutamine. As the metabolic utilisation rate of glutamine is higher than the synthesis rate in physiological stress conditions such as surgical procedures, sepsis, cancer cachexia and burns, the plasma and intracellular glutamine concentrations decrease, and glutamine becomes essential. (8, 9, 12). This facilitates the expression of inflammatory cytokines (13). According to the recommendations of ESPEN (European Society for Clinical Nutrition and Metabolism) and ASPEN (American Society for Parenteral and Enteral Nutrition), intravenous glutamine support for total parenteral nutrition in critically ill patients is recommended at level A. In meta-analyses, 0.3-0.5 g/kg glutamine per day to parenteral nutrition is indicated to take plasma glutamine concentration to normal levels in critically ill patients. (14). In the ESPEN guideline, administration of immunonutrition formulas to malnourished patients undergoing major cancer surgery in the perioperative period or, if not, in the postoperative period, is recommended at level B. (15).

Arginine

Arginine is a semi-essential amino acid that plays a role in nucleotide synthesis, the synthesis of polyamine, proline and hydroxyproline, which have a function in connective tissue repair, and the synthesis of nitric oxide (NO), which is an important signalling molecule in many metabolic pathways (9, 16). Nitric oxide regulates protein synthesis in the liver, causes vasodilation, and creates an anti-inflammatory effect by reducing the release of inflammatory substances (11). The bactericidal characteristic of NO is also crucial in leukocytes and macrophages' phagocytosis of pathogenic bacteria in the body. Arginine supports cellular immunity by increasing Interleukin 2 (IL-2) production and T cell proliferation and by stimulating Natural killer (NK) cell activity activated by lymphokines (17). Arginine regulates lymphocyte function in the body and promotes wound healing by stimulating collagen synthesis (9, 16, 18). In clinical studies evaluating the effects of enteral arginine support, it has been shown that net nitrogen uptake and protein synthesis increase, and wound healing improves. Therefore, arginine helps to develop systemic inflammatory responses caused by the unbalanced release of NO (13). Although it is not essential in normal healthy individuals, it becomes essential in catabolic conditions such as cancer, surgery and trauma (9). The half-life of arginine is longer when given orally, so the oral route should be preferred for long-term treatment. In healthy individuals, 30 g of arginine per day is well tolerated. Abdominal cramps, nausea, vomiting, and diarrhoea may occur if more than forty grams are taken (19). Despite that, arginine support may be detrimental in sepsis due to the high NO levels seen in the models of animal endotoxemia and septic shock (20).

Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated with two different bioactive forms in humans: eicosapentaenoic acid (EPA; 20:5, w-3) and docosahexaenoic acid (DHA; 22:6, w-3). EPA and DHA fatty acids are synthesised in the body from α-linolenic acid (ALA, 18:3, w-3), an essential fatty acid (21). While ALA is found in nuts and oil seeds, EPA and DHA are the main components of fish oil (22). Omega-3 fatty acids regulate the structural and functional integrity of the cell membrane, provide intercellular signal transmission, and play a role in the synthesis of eicosanoids, an important immune mediator. Omega-3 fatty acids, obtained from fish oil, suppress the production of inflammatory prostaglandin and prostacyclin by replacing arachidonic acid (AA, 20:4, w-6) produced from omega-6 fatty acids in immune cell membranes and thus enable to reduce the cytotoxicity of inflammatory cells (13). EPA and DHA fatty acids reduce the production of inflammatory cytokines interleukin-1, interleukin-6 and tumour necrosis factor (TNF) by promoting the production of prostaglandin 3 and leukotriene 5 series among eicosanoids (23). It has been stated that omega-3 fatty acids inhibit the COX-2 enzyme from the cyclooxygenase (COX) enzyme family; thus, it has an anti-inflammatory effect by reducing the production of PGE2 (prostaglandin E2), which increases inflammation (24) (Figure 2). EPA and DHA fatty acids are also precursors of resolvin mediators. Resolvin mediators help reduce cellular inflammation by inhibiting inflammatory cell migration and mediators (13). In recent years, it has been investigated that omega-3 fatty acids may also influence immune system cells. It is thought that ALA, EPA and DHA can increase the phagocytic capacity of macrophages. In studies investigating the effect of omega-3 fatty acids on neutrophil cells, it has been stated that EPA and DHA have a positive effect on the immune system by increasing the frequency and phagocytic capacity of neutrophils (22). It has been shown that orally taken omega-3 fatty acid supplements are included in the cell membranes and metabolised after a few weeks of use, and this time is reduced to a few days in parenteral administration (17).

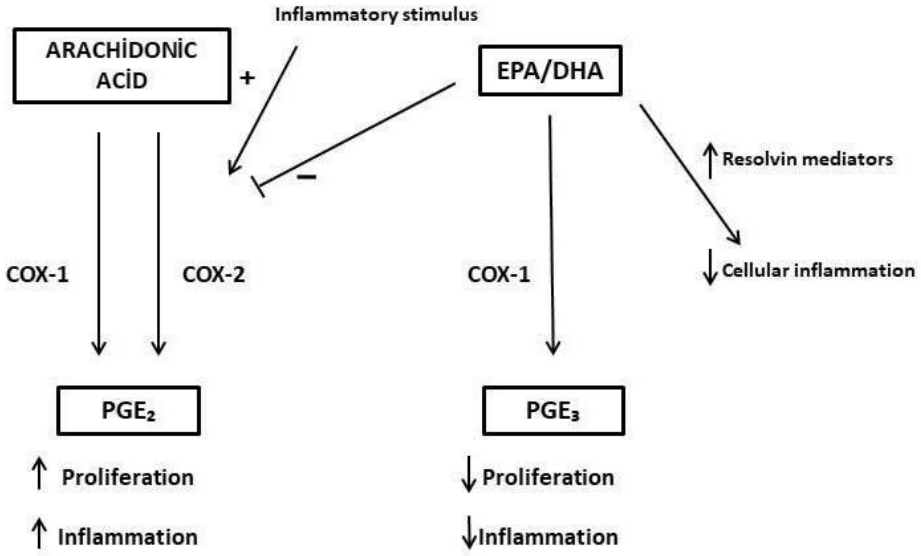

Figure 2. COX (cyclooxygenase) effect of the enzyme family on w-6 and w-3 polyunsaturated fatty acids, arachidonic acid and EPA/DHA (adapted from source number 23)
COX, cyclooxygenase; PGE2, prostaglandin E2; PGE3, prostaglandin E3

RNA Nucleotides

RNA nucleotides are involved in the structure of DNA and RNA. It functions in many metabolic pathways such as energy metabolism, signal transduction, glycogen and phospholipid biosynthesis, regulation of enzyme activity, maintenance of intestinal mucosal integrity, tissue repair and cell regeneration (8, 11). Since nucleotide synthesis requires excessive energy in the case of metabolic stress, it is important to supply it from outside.

As the need for nucleotides is high in rapidly regenerating tissues and cells (enterocytes, lymphocytes, macrophages, Etc.), its deficiency leads to immune deficiency (11, 25). In animal experiments, it has been shown to improve T cell functions, antibody response, delayed-type hypersensitivity, and resistance to pathogens (8). It has been reported to regulate the lymphocyte proliferation of nucleotides and their metabolites and affect the immune function dependent on macrophages and natural killer cells (4). It has been shown that interleukin 2 production and T cell response is reduced due to a diet deficient in RNA nucleotide (26).

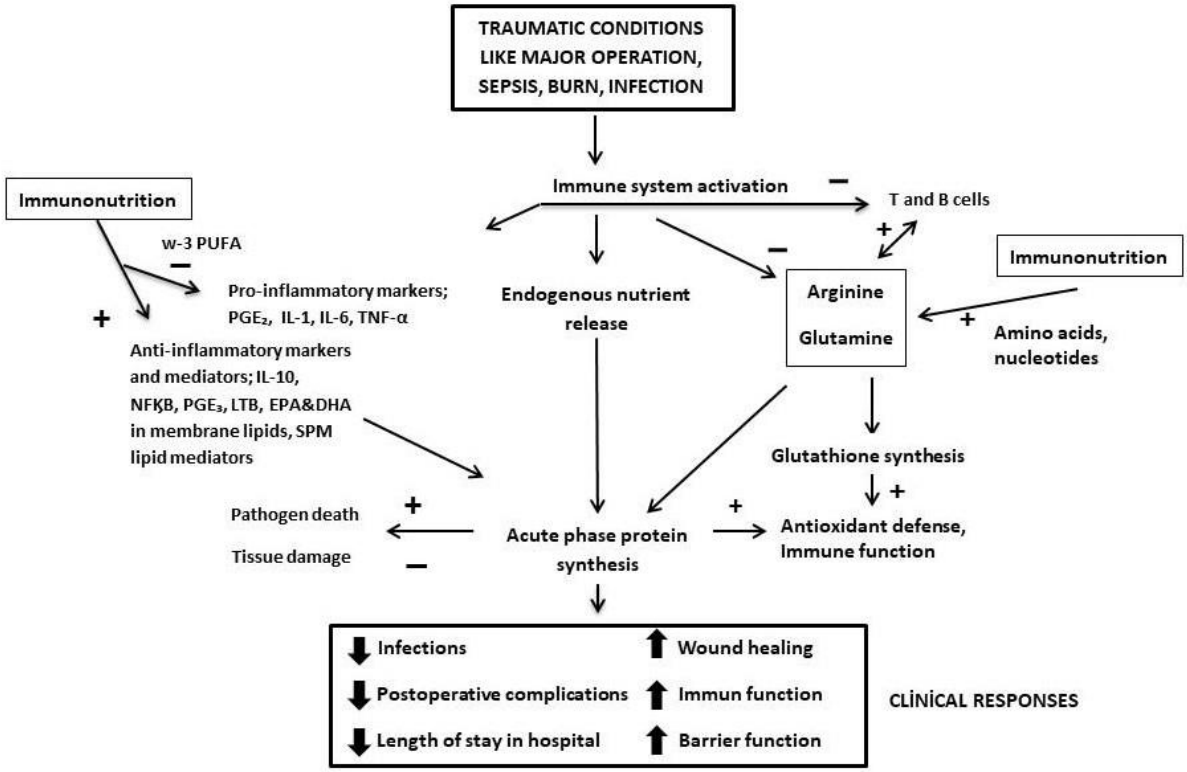

Figure 3. Overview of the impact of immunonutrition on the immune response (Adapted from source number 5) PUFA, polyunsaturated fatty acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IL, interleukin; LTB, leukotriene B series; NFKβ, nuclear factor kappa β; PGE, prostaglandin E series; SPM, specialized resolving protein; TNF-α, tumor necrosis factor-α; +, stimulating effect; -, negative effect

The Importance of Medical Nutritional Treatment in Lung Cancer

The clinical indicators of lung cancer are complex; the tumour's location, complications, metastasis status, and cell type affect the lung cancer stage. In early-stage lung cancer, atypical clinical symptoms such as cough, chest pain, and hoarseness are observed. For this reason, the rate of misdiagnosis is high in the early stage, and most patients are diagnosed in the advanced stage, which is late for treatment (10).

Lung cancer can be divided into two main categories: small cell lung cancer and non-small cell lung cancer (27). Non-small cell lung cancer accounts for approximately 85% of all cases (28). The treatment depends on the lung cancer stage and the tumour's characteristics. Surgery, chemotherapy, radiotherapy or chemoradiotherapy are both applied as treatment (3).

While metabolic status, disease-induced inflammation, and cancer treatments, which vary according to the characteristics of the tumour, cause to increase in the body's energy and nutrient needs, the treatment methods applied to the patient adversely affect the patient's appetite, food intake and use of nutrients in the body by generally causing nutritional problems such as nausea, vomiting, loss of appetite, mucositis, early satiety, diarrhoea, and constipation. Despite the increase in energy and protein needs, negative energy and nitrogen balance occurs due to decreased food intake with loss of appetite and inability to meet the increasing losses (29). As a result, malnutrition, cachexia, or sarcopenia can be seen due to severe weight loss in patients. Weight loss may adversely affect the patient's metabolic response to treatment, quality of life and survival. Therefore, it is of great importance to evaluate the nutritional status of patients from the moment of diagnosis and to provide patient-specific nutritional support when necessary. In patients who cannot be fully fed orally, appropriate oral, enteral product support should be provided, and tube feeding or parenteral nutrition should be started when necessary (30).

The Role of Immunonutritional Support in Medıcal Nutritional Therapy for Lung Cancer

Studies on immunonutrition in the literature are generally associated with gastrointestinal system cancers and head and neck cancers. Studies on the effect of immunonutritional support on lung cancer are very limited. In a study examining patients with lung cancer after lobectomy, patients were divided into two groups; conventional treatment was applied to the control group, while the experimental group received an intravenous (IV) infusion of 100 ml of glutamine twice a day for 7 days in addition to the conventional treatment. The postoperative infection rate, endotoxin and TNF-α levels were found to be significantly lower in the group taking glutamine compared to the control group. While serum IL (interleukin)-1 and IL-10 levels were found to be significantly higher in the experimental group compared to the control group, serum IL-15 and IL-18 levels were found to be low. In addition, the expression level of intercellular adhesion molecule 1 (ICAM 1) and myeloperoxidase (MPO) activity were found to be higher in the experimental group. In the group receiving IV glutamine supplement, the duration of bed rest and hospital stay after the surgery were found to be significantly shorter compared to the control group. As a result of the study, it was stated that glutamine supplement after lobectomy improves postoperative lung functions, regulates IL-1 and TNF-α levels of glutamine, reduces bed rest and hospital stay, and increases patients' quality of life (10). In his study, Topkan et al. determined that glutamine was beneficial in preventing weight loss and unplanned treatment disruptions in the nutritional support group, and it reduces the incidence and severity of radiation-induced esophagitis in the acute and late period as a result of oral glutamine (30 g/day) support given to advanced lung cancer patients receiving chemoradiotherapy (31).

In a prospective study investigating the effect of oral glutamine powder supplement (30 g/day) starting 1 week before radiotherapy and administered until 2 weeks after the end of the treatment on radiotherapy-induced acute esophagitis in lung cancer patients receiving radiotherapy (n=32), it was reported that oral glutamine use prevented or delayed acute esophagitis while the toxic effect status of radiotherapy, weight loss, serum cytokine levels and oesophageal transit time were better in the group taking glutamine (32, 33). In another study on this subject, patients who received chemoradiotherapy were followed for an average of 26.4 months, and a decrease in the incidence of acute radiation-induced 2nd and 3rd stage esophagitis was observed in the group receiving oral glutamine supplements. It was found that glutamine supplements reduced the duration of esophagitis by an average of 5.8 days (p=0.027), and the incidence of weight loss was between 20% and 73.3% (p=0.01) (34). In patients with lung cancer who received oral glutamine supplements (30 g) and received thoracic radiotherapy, the stage of radiotherapy-induced esophagitis was found to be lower than in patients who did not receive oral glutamine supplements (p<0.001) (35).

The omega-3 fatty acid supplement was applied to patients with advanced lung cancer for 6 weeks, and while CRP and IL-6 levels were found to be better in the group taking omega-3 supplement compared to the control group, no difference was found in terms of nutritional status and quality (36). In another multicentred, randomised, double-blind study, 510 mg of EPA and 340 mg of DHA fatty acids were given to patients with advanced lung cancer receiving chemotherapy, and biochemical parameters and anthropometric measurements were checked at the beginning of chemotherapy, on the 8th day, on the 22nd and 66th days. Body weight on the 66th day in the experimental group was found to be significantly higher than at the beginning of chemotherapy. In addition, while CRP and IL-6 levels on the 66th day were lower in the experimental group during the chemotherapy process, the level of plasma reactive oxygen species was higher in the placebo group. While hydroxynonenal levels increased in the placebo group during the study period, they remained stable in the omega-3 group. This study drew attention to the anti-inflammatory and anti-oxidative effects of omega-3 fatty acid supplements during the chemotherapy process (37). In the meta-analysis investigating the effect of omega-3 fatty acids on cancer cachexia in patients with advanced lung cancer, 6 studies (394 patients in total) were analysed, and it was found that omega-3 fatty acid supplements significantly increased body weight and quality of life score in patients (38). In the randomised, double-blind study of Van der Meij et al., oral nutritional support containing omega-3 fatty acids (2 g EPA and 0.9 g DHA) was administered to stage 3 lung cancer patients, and the preservation of body weight after 2-4 weeks and the preservation of lean body mass after 3-5 weeks were found to be better in the intervention group (p<0.05). In addition, while the resting energy expenditure was found to be lower in the third week after the intervention in the group receiving omega-3 fatty acids (p=0.01), it was determined that the upper middle arm circumference was higher (p=0.06), and IL-6 levels were lower at the 5th week (p=0.08). It was stated that energy and protein intake was higher in the intervention group compared to the control group after 4 weeks (p=0.01) (39). Within the scope of the same study, quality of life parameters, physical and cognitive functions (p<0.01), health status (p=0.04) and social functions (p=0.04) were found to be better in the intervention group compared to the control group after 5 weeks. (40). In the study in which the performance levels of patients with advanced lung cancer were investigated, the average Karnofsky performance status (KPS) level of the patients was found to be 74.2±11% using the KPS scale (41). In another study in which Karnofsky's performance status was used, while KPS level was found to be higher after three weeks in the group receiving omega-3 fatty acids, physical activity status was reported to be higher both at the end of 3 weeks and the end of 5 weeks compared to the control group (40).

Patients with non-small cell lung cancer who will undergo lung cancer surgery were given immunonutrition support containing arginine, omega-3 fatty acids and nucleotide for 10 days before surgery, and it was determined that there were fewer postoperative complications in the experimental group compared to the patients in the control group who did not receive any nutritional products and continued only on their usual diet, and chest tube drainage time was shorter (p<0.05). While serum albumin levels of the patients in the control group decreased by 25.71% on the third postoperative day compared to the beginning, this level was found at 14.69% in the experimental group (p<0.001) (42).

In a retrospective study investigating the effect of immunonutrition on patients undergoing lung cancer surgery, the patients in the experimental group were given nutritional support, including arginine, glutamine, omega-3 fatty acids and RNA 7 days before the operation, and they were used for 15 days after the operation. No nutritional support was given to the control group. The incidence of postoperative complications and length of hospital stay was significantly lower in patients receiving nutritional support (43).

CONCLUSION

Decreased oral intake due to disruption of the normal anabolic process in lung cancer patients, side effects of cancer treatments, and in parallel with this early satiety, pain, fatigue, psychosocial factors, and factors such as various gastrointestinal problems affect patients' nutritional status and consequently the course of the disease and survival negatively. Therefore, the nutritional status of lung cancer patients should be evaluated and followed up in detail from the time of diagnosis, and nutritional support treatment should be initiated when necessary. In the treatment process, immunonutritional support can support the immune system and reduce the inflammatory effects of the disease and cancer treatments in the body. In clinical studies and applications, positive effects of immunonutritional support are observed in preventing possible infections and cancer-related inflammation, on the duration of hospitalisation and wound healing during the treatment process, especially on esophagitis and mucositis due to radiotherapy. Nutritional support should be started from the moment of diagnosis, and cancer treatments should be supported by medical, nutritional therapy. Especially in patients who will undergo lung cancer surgery, nutritional support should be started orally, enterally and/or parenterally 7-10 days before the surgery. It should be continued with early enteral nutrition after the surgery until the patient receives adequate nutrition orally. In addition to these positive effects, the action mechanism of each of the immunonutrients has not been fully explained due to the lack of well-conducted clinical studies in lung cancer. In addition, there are uncertainties about the optimal amounts to take of each of the immunonutrients in the nutritional solutions in the market, the interactions that may occur with the agents used in the treatment, the toxic effects that may occur due to excessive intake, and the optimal combinations of nutrients. More evidence-based, well-conducted clinical studies are needed to clarify the specific effects of immunonutrients during lung cancer treatment. Immunonutritional nutrition therapy applications to patients should be carried out following the recommendations of current nutrition guidelines.

Conflict of interest
No conflict of interest was declared by the authors.

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