



Nutritional issues in patients with cancer

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Cancer is a catabolic inflammatory disease that causes patients to often experience weight loss, or even cachexia in severe cases. Undernourishment in patients with cancer impairs the quality of life and therapeutic response, further leading to poor prognosis. Active and frequent nutritional screening and assessment using valid tools are important for fast and appropriate nutritional intervention. Additionally, a suitable individualized nutritional intervention strategy should be established based on the nutritional assessment result. In general, nutritional intervention begins with nutritional counseling of patients diagnosed with cancer, and a well-planned nutritional counseling improves the treatment adherence and nutritional status. When planning nutritional supplementation for cancer patients, specific nutrients, including amino acids and fatty acids, should be considered. However, there has been no consistent result showing that any particular nutrient significantly improves the prognosis of cancer patients. Hence, continuous attention from clinical physicians is needed to plan nutritional improvement in patients with cancer. (**Intest Res 2019;17:455-462**)

Key Words: Neoplasms; Nutrition assessment; Nutrition therapy

INTRODUCTION

Nutritional problems are often encountered during the treatment of cancer. A prospective observational study reported that 51.1% of all cancer patients presented nutritional impairment, and 64% of patients showed reduction in weight 6 months after diagnosis.¹ Weight loss, especially cachexia, are widely recognized as not only reduced physical function and quality of life, but also poor prognostic factors in cancer patients. Classically, BMI is often used for measuring nutritional status of a patient, and recent studies have focused more on sarcopenia.² However, nutritional problems are complex and vary depending on the location and stage of cancer.^{1,3} Therefore, nutritional support for cancer patients should be based on the assessment of each patient's condition and appropriate planning of the outcome. In this review, we will look at what should be consid-

ered to prevent malnutrition by providing adequate nutrition to cancer patients.

ALTERATION OF ENERGY METABOLISM IN CANCER PATIENTS

Cachexia, commonly seen in cancer patients, is not simply caused by malnutrition due to anorexia. It is a more complex condition including reduced intake, metabolic dysfunction, and increased energy requirement. This process involves a variety of inflammatory cytokines in cancer cells, alterations in protein and lipid metabolism, and an imbalance in the production and degradation processes of muscle proteins.

Dysfunction in the regulation of human inflammatory process is observed in several diseases, including cancer. Researches have shown that increased inflammatory cytokines, such as TNF- α and interleukin-6 (IL-6), play critical roles in the nutritional metabolism of cancer patients.⁴ TNF- α is a cytokine related to cachexia, and it was originally called cachectin.⁵ It has long been known that TNF- α infusion causes loss of skeletal muscle mass in mice, and TNF- α blocking immunoglobulin

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reduced muscle loss in tumor-bearing rats.^{6,7} Although it is controversial if TNF- α levels in blood are higher in cancer patients, it is believed that TNF- α activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and promotes the degradation of proteins through a pathway independent of the ubiquitin-proteasome pathway.⁸ Furthermore, TNF- α activates other cytokines and can cause symptoms associated with cachexia, such as anorexia.⁹ A study using an anti-TNF- α agent, etanercept, in cancer patients reported that etanercept improved chemotherapy adherence and fatigue during cancer treatment.¹⁰ IL-6 is also believed to play a very important role in cancer-related cachexia. In a study using *ApcMin/+* mice, elevation of IL-6 did not induce cachexia in the tumor-free mice. However, elevation of IL-6 was associated with decreased skeletal muscle and fat mass, and increased tumor burden in *ApcMin/+* mice.¹¹ In cancer patients, IL-6 increases the acute phase reactants such as CRP through signal transducer and activator of transcription 3 (STAT3), and it is associated with muscle wasting.¹² However, in a study of lung cancer patients, administration of humanized anti-IL-6 antibody was effective in alleviating symptoms such as anorexia, but it did not induce weight gain.¹³ Therefore, it is observed that cancer-associated cachexia is not simply related to one cytokine, but is influenced by the interactions of various signaling substances.

In catabolic diseases, various hormones and cytokines regulate protein production and degradation through the ubiquitin-proteasome pathway, autophagy, and transforming growth factor beta family ligands. Up-regulation of the ubiquitin-proteasome pathway by catabolic stress in several animal tumor models has been associated with muscle wasting. Myofibrillar components of muscle protein are mainly disintegrated in the ubiquitin-proteasome pathway, and this leads to decreased muscle strength.¹⁴ Moreover, the stress hormones and inflammatory cytokines promote autophagy and mitochondrial dysfunction, which lead to muscle atrophy. These processes are regulated by atrogenes and transcription factors, such as NF- κ B and forkhead box protein O (FOXO).¹⁴ Especially in cancer patients, chemotherapy itself and malabsorption by complications of chemotherapy, such as mucositis, can directly induce muscle wasting.¹⁵

It is well known that impairment of carbohydrate metabolism occurs in cancer patients. Cancer cells show high glycolysis, and glucose is produced by gluconeogenesis in the liver using lactate produced by the cancer cells.¹⁶ During cancer-associated cachexia, increased level of insulin-like growth factor-1 is observed, resulting in insulin resistance.¹⁷ Thus, most

of the glucose induced is used by the cancer cells; hence, cancer patients have a very high energy demand. However, in actual clinical studies, insulin resistance is not inevitably associated with weight loss.¹⁸

Lipid metabolism is also impaired in cancer patients. The loss of adipose tissue by metabolic impairment further promotes cancer-associated cachexia. The accumulation of triglycerides in the cytoplasm of adipocytes is the most efficient method of energy storage. Free fatty acid and glycerol from triglyceride increase in patients with cancer-associated cachexia.¹⁹ Higher lipolysis and fat oxidation rates were observed in cancer patients losing weight as compared to that of healthy control.²⁰ This lipolysis was promoted by hormones, pro-inflammatory cytokines, and lipid-mobilizing factor.²¹ One interesting finding of lipid metabolism in cancer patients is fat browning. White adipose tissue cells convert to brown adipose tissue-like cells (beige cells) during cancer-associated cachexia, similar to the mechanism in cold environments.²² The abundant mitochondrial components of beige cells produce heat (thermogenesis) from ATP synthesis through increased uncoupling protein-1.¹⁷ Fat browning in cancer-associated cachexia represents imbalance of homeostasis and contributes to catabolic wasting unlike normal physiologic conditions.

IMPACT OF MALNUTRITION ON TREATMENT OUTCOMES IN CANCER PATIENTS

Although the stage and type of cancer and the response to chemotherapy are the most important prognostic factors, many studies have reported that patients who maintained weight gain presented better prognosis than those who did not. Malnutrition is associated with longer hospital stay and higher rate of admission, delayed wound healing, deterioration of the immune system, and cancer-associated death.²³⁻²⁵ An important association beyond just cause and effect has been elucidated between malnutrition and aggravation of the disease. In a multicenter study investigating the prevalence of malnutrition in patients during cancer treatment, old age, hospital stay, and metastasis showed an association with malnutrition. Moreover, malnutrition was associated with higher infection rate and longer hospital stay;²⁶ therefore, mere focus on increasing the weight of cancer patients does not affect the patient's clinical prognosis positively.

Sarcopenia in patients with cachexia has recently been noted for contributing to poor prognosis in cancer patients. In a study that investigated prognosis of patients with cholangio-

carcinoma after major surgery, preoperative sarcopenia was associated with longer hospital stay, higher rate of liver failure, and higher postoperative infection rate.²⁷ Sarcopenia showed positive association with increased toxicity from chemotherapy and faster tumor progression in patients with metastatic breast cancer,²⁸ and was related to lower survival rate. In a retrospective study analyzing 229 stage III colon cancer patients, one standard deviation decrement of the psoas muscle mass index was related to an increased hazard of overall mortality in multivariate analysis.²⁹ Likewise, in a prospective study of patients with foregut cancer treated with neoadjuvant chemotherapy, loss of skeletal muscle mass was a predictor of reduced survival rate.³⁰ Several other studies of different cancer types reported that sarcopenia adversely affected the prognosis associated with cancer treatment and was associated with complications.

The quality of social, psychological, and physical life can be greatly reduced because of the cancer pathology itself. The nutritional status of a cancer patient is influenced by the quality of life, because weight loss and decreased appetite are significantly related to the quality of life.^{31,32} However, the poor quality of life in cancer patients is not solved simply by improving the nutritional status. A prospective randomized control trial showed that dietary intervention involving regular nutritional counseling in patients with solid tumor during chemotherapy was not significantly related to a better quality of life as compared to the control. The results were consistent even if the patients had better nutritional status through nutritional counseling. The quality of life considerably improved in patients with significant tumor regression.³³ These results show that the relationship between cancer, malnutrition, and quality of life is complex.

NUTRITIONAL SCREENING AND ASSESSMENT IN CANCER PATIENTS

Assessing weight loss in cancer patients has been used since long as the simplest and most effective way to determine malnutrition. Although BMI can be disturbed by ascites and body edema, many studies showed that BMI and unintended weight loss were the methods used to monitor malnutrition in patients and predict poor prognosis. Even though various nutritional assessment tools have been introduced and actively used, BMI still plays an important role. A study investigating 3,779 patients with colorectal cancer, between 1972 and 2017, revealed that the underweight group showed a significantly worse overall

survival rate as compared to the normal weight group in stage III and IV cancer patients. More than 10% of weight reduction from pre-diagnosis to post-diagnosis showed a significant relation with poorer overall survival.³⁴ Moreover, in a prospective study analyzing 82 metastatic breast cancer patients from 2011 to 2012, overweight patients showed a significant association with lower rate of cancer mortality as compared to the normal weight patients.³⁵ Excessive nutrition is not recommended when considering the overall disease mortality including metabolic diseases. Furthermore, the prognosis is worse in overweight patients when there is accompanied muscle loss. Thus, it is obvious that simply maintaining the weight could play a protective role against cancer mortality.

Traditionally, serum concentrations of liver proteins, such as albumin, have been associated with the nutritional status of patients. Therefore, a lack of these proteins indicated undernourishment and was used as an indicator of active nutritional support.³⁶ However, since albumin has a long half-life and is inhibited by inflammatory cytokines including TNF- α and IL-6, which are elevated in cancer patients, it cannot be an immediate and accurate indicator of malnutrition.³⁷

Nowadays, instead of using only 1 specific parameter to evaluate the patient, several factors are combined to assess the nutritional risk and evaluate the nutritional status. The Malnutrition Universal Screening Tool, Nutrition Risk Screening 2002, Mini Nutritional Assessment Short Form, and Malnutrition Screening Tool are validated and widely-used nutritional risk screening tools.³⁸ The purpose of nutritional risk screening is to emphasize the importance of nutritional support and promote early intervention to ultimately prevent poor outcomes due to malnutrition. Therefore, these screening tests should be easy to apply and interpret. Although they have different target patients, all the screening tools use parameters of BMI, weight change, accompanying disease, and degree of food intake.³⁹ The strategy for screening nutritional risk in cancer patients should adopt an individualized strategy for each medical institution considering the applicability of each tool. Although there is a lack of clear evidence eliciting the clinical benefits of nutritional screening tools in cancer patients, no studies have proved the inefficacy of nutritional risk screening tools.⁴⁰⁻⁴² In fact, there are certain benefits of screening for nutritional risk depending on the type and treatment of cancers. Therefore, the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline recommends that there should be regular evaluation of nutritional intake, weight change, and BMI, that starts during cancer diagnosis and is repeated depending on the stability of

Table 1. Nutritional Screening and Assessment Tools

Tool	Evaluation item
Screening tool	
Malnutrition Universal Screening Tool	BMI (kg/m ²), weight loss (%), nutritional intake
Nutrition Risk Screening 2002	Initial screening: BMI (kg/m ²), weight loss (during 3 months), nutritional intake (during a week), disease severity Final screening: impaired nutritional status (score), disease severity (score), age (additional score)
Mini Nutritional Assessment Short Form	Food intake, weight loss, mobility, psychological stress, neuropsychological problems, BMI (kg/m ²), calf circumference (cm)
Malnutrition Screening Tool	Weight loss, appetite
Assessment tool	
Patient-generated-subjective global assessment	Patient: weight, symptom, nutritional intake, activity Medical staff: diagnosis, nutritional requirement, physical examination
Nutrition Risk Index	$(1.519 \times \text{serum albumin, g/dL}) + (41.7 \times \text{present weight [kg]} / \text{ideal body weight [kg]})$

the clinical situation.³⁹

If the patient is predisposed to have a nutritional risk, an assessment of the patient's nutritional status must be performed. Comprehensive nutritional assessment provides an objective goal for individualized nutritional care of the patients, ultimately improving the clinical outcomes by protecting the patients from treatment complications, and improving both the treatment outcomes and quality of life. Therefore, the nutritional assessment of cancer patients should be repeated periodically, and not just once. There are many nutritional assessment tools used in researches and clinical practice. Although each nutritional assessment tool varies slightly, most tools consist of the patient's medical history, food intake, physical activity level, weight change, other anthropometric measures, and laboratory test results.⁴³ Among the various tools available, the patient-generated-subjective global assessment (PG-SGA) has been developed specifically for cancer patients. PG-SGA is a tool that evaluates the clinical aspects, including physical examination and accompanying diseases, and confirms the change in the patient's weight or dietary intake, presence or absence of gastrointestinal symptoms that may affect the dietary intake, and expresses a numerical score.⁴⁴ The start and posttreatment follow-up of nutritional intervention are based on this score. PG-SGA is a valid and dependable tool that provides a reference to identify and classify the nutritional state of a cancer patient. Nutrition Risk Index is another commonly used assessment tools.^{45,46} Reduced muscle mass can be measured objectively using dual X-ray absorptiometry, CT scans, or bioimpedance analysis (Table 1).

NUTRITIONAL INTERVENTIONS

When a patient is diagnosed with cancer for the first time, the doctor should pay special attention to nutrition to prevent the patient from following detrimental diets. Doctors, as scientists, are naturally alert towards non-evidence-based treatments and excessive dietary imbalances, such as fad diets, that have a negative impact on the financial state as well as on the clinical prognosis. A fad diet is an alternative medicine comprising of extremely high or low intake of certain foods, which will most likely result in nutritional imbalance. Furthermore, there is no strong evidence supporting the beneficial effects of the fad diets on cancer treatment.³⁹ Cancer patients are mentally vulnerable and tend to be obsessed with food control, and thus the patient could actively intervene in the cancer treatment process. Hence, doctors treating cancer should understand the characteristics of these patients and implement appropriate interventions. Nutritional counseling and diet advice are therefore very important in cancer patients at nutritional risk during diagnosis, and these can be conducted from 3 perspectives. First, the amount of food consumed should be increased. Second, the composition of the food should be balanced along with high-energy intake from a nutritional point of view. Third, nutritional supplements that can be ingested orally should be considered.⁴² Cochrane review reported that nutritional counseling had a beneficial effect on improving the weight reduction and quality of life in patients with cancer by analyzing randomized controlled trials.⁴² In addition to nutritional counseling, there have been studies wherein patients who consumed oral nutritional supplements demonstrated

better weight gain than those who did not. A systematic review and meta-analysis of 13 studies reported that oral nutritional interventions had a beneficial effect on the quality of life.⁴⁷ On the other hand, another meta-analysis showed that oral nutritional supplementation improved the quality of life of patients but did not reduce the mortality in cancer patients.⁴⁷

From the perspective of overcoming sarcopenia, high-protein diets can be considered. Patients with acute or chronic diseases need 1.5 g/kg of protein per day, but one study found that 35% of cancer patients consumed fewer proteins than required.^{48,49} A randomized, controlled, double-blind, parallel-group designed study using experimental high-protein diet in cancer patients revealed that the high-protein diet group showed significantly better muscle synthesis than the control group.⁵⁰ Although leucine is the most important amino acid in muscle synthesis, there are no consistent results showing that high doses of leucine will help prognosis in patients with cancer. Moreover, a recent experimental study showed that high level of leucine could induce tamoxifen resistance in estrogen-receptor positive breast cancer patients.⁵¹ Therefore, when using high dose of a specific nutrient, a thoughtful evaluation is necessary. Glutamine is also considered a nutritional supplement for cancer patients. Glutamine is a nonessential amino acid that serves an important role in the metabolism and immune system. Glutamine levels are reduced in cancer patients because glutamine is used as the energy source by cancer cells. Glutamine supplementation is usually focused on preventing side effects that may occur during chemotherapy or radiotherapy, especially in gastrointestinal mucosal protection. A prospective study investigating the beneficial effect of a parenteral glutamine supplementation in 24 metastatic colorectal cancer patients during chemotherapy revealed that glutamine supplementation was associated with a significant reduction in mucositis and ulceration of the upper gastrointestinal mucosa.⁵² However, additional prospective studies are needed to determine the relationship between prognosis and glutamine supplementation in cancer patients and the effect of oral and intravenous glutamine.

Omega-3 fatty acids can also be expected to provide nutritional supplementation in cancer patients. Unlike omega-6 fatty acids, omega-3 fatty acids have anti-inflammatory effects and do not promote angiogenesis.⁵³ Therefore, supplementing omega-3 in cancer patients has the advantage of providing nutrition, especially fat, without stimulating tumor growth. In some studies,^{54,55} omega-3 supplementation was shown to help weight gain in cancer patients, while other systematic re-

view studies showed that there was unclear evidence of the beneficial effect of omega-3 in improving cachexia in cancer patients.^{56,57} However, since the intake of omega-3 fatty acids rarely causes serious adverse effects, the ESPEN guideline recommended supplementing omega-3 fatty acids in cancer patients having weight loss.³⁹

CONCLUSION

There is a lack of attention towards the nutritional status of cancer patients in clinical practice. However, monitoring and intervention of nutritional status not only affect the quality of life of the patient, but also the treatment response and clinical outcomes. Since no strategy particularly good at improving the nutritional status in cancer patients has yet been developed, it is important that individualized treatments be performed for each patient according to their nutritional assessment. Moreover, continuous vigilance regarding factors affecting nutritional status in patients with cancer is necessary.

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CONFLICT OF INTEREST

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