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High PUFA Oral Nutritional Supplementation's Effect on Advanced Cervical Cancer Patients' Nutritional Status

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Abstract: While weight loss occurs in patients with cancer, PUFA may suppress cancer growth. This study aims to determine the high PUFA nutritional supplementation's effect on the nutritional status of patients with advanced cervical cancer who received radiotherapy. This study was a double-blind Randomized Clinical Trial on patients with advanced cervical cancer. Subjects were taken consecutively, through randomization, divided into treatment and control groups. Thirty-one patients were involved as respondents, with 16 in the treatment groups and 15 in the control groups. The findings revealed that socio-demographic status, omega-6 and omega-3 fatty acid intake patterns, and nutritional and clinical status were not significantly different between groups before treatment. Nutritional supplementation was provided as ONS labeled A and B, taken three times a day. During treatment, patients were asked to record all food and beverages consumed in the intake book at least three days a week, including two working days and one day off. The treatment group's body weight was relatively more stable, while the control group tended to decrease in weight, but the Δ weight loss in each group was not significantly different ($p = 0.149$). PUFA supplementation can maintain the nutritional status of patients with cervical cancer by maintaining body weight.

Keywords: polyunsaturated fatty acids; body weight: cervical cancer; radiotherapy

INTRODUCTION

Cervical cancer is one of the leading causes of cancer deaths in women. According to the Global Burden of Cancer (Globucan) data published by the World Health Organization (WHO), the total cases of cervical cancer worldwide in 2020 reached 604,127, with a total mortality of 341,831. The incidence of cervical cancer in Indonesia in 2020, according to WHO, was 36,633 cases, constituting 9.2% of all cancer cases and ranking second after breast cancer.[1] Cervical cancer caused by human papillomavirus (HPV) infection, characterized by abnormal growth or cell changes in the cervix.[2,3] Abnormal changes cause several symptoms, including vaginal bleeding, lower abdominal pain, pain during sex, and vaginal discharge.[3]

The recommended treatment for patients with cervical cancer is chemotherapy or radiotherapy. Patients with cervical cancer undergoing radiotherapy treatment will experience radiation therapy side effects that vary depending on the treatment dose and the patient's general condition. Some of the side effects include fatigue, skin reactions (dryness, redness, pain, discoloration, and ulceration), decreased blood cells, diarrhea, nausea, vomiting, and loss of appetite, leading to a decrease in body weight (BW) and poorer nutritional status.[4] The decrease in nutritional status is more pronounced in patients with higher stages of cancer.[5]

Decreased appetite leads to dramatic weight loss, resulting in cachexia, which is an imbalance between food intake and increased nutrient requirements. Prolonged cachexia will lead to malnutrition. As many as 20-50% of patients with cancer have nutritional problems, one of which is malnutrition.[6] Malnutrition or cachexia generally occurs in patients with early-stage cancer (24%) and advanced-stage (>80%).[7] Malnutrition has side effects for patients, including reducing the effectiveness of drugs used during chemotherapy.[8] Malnutrition can be overcome by nutritional interventions (including the use of food supplements), nonpharmacological therapy (nutritional counseling, education, psychotherapy, and physical training), and pharmacological therapy.[9]

On the other hand, Polyunsaturated fatty acids (PUFA) include omega 3 alpha-linolenic acid (ALA), eicosatetraenoic acid (EPA), docosahexaenoic acid (DHA), omega 6 linolenic acid (LA), and arachidonic acid (AA). Omega-3 and omega-6 are essential fatty acids that the body cannot produce so they must be fulfilled from food intake.[10] EPA and DHA are precursors of anti-inflammatory lipid mediators, while AA is a precursor of pro-inflammatory lipid mediators. In general, PUFA plays a vital role in maintaining cellular homeostasis, and disturbances in diet or PUFA metabolism may lead to cellular dysfunction and contribute to cancer risk and progression.[11]

In vitro and in vivo studies have exhibited that PUFA has differential properties concerning cancer. Consumption of omega-3 PUFA can suppress inflammation, stimulate apoptosis, inhibit tumor metastasis and proliferation, and upregulate gene expression of antioxidant enzymes. Nevertheless, consumption of omega-6 PUFA has a carcinogenic effect that correlates with an increase in the eicosanoid ratio.[12] Hence, this study aims to determine the effect of high PUFA nutritional supplementation on the nutritional status of patients with advanced cervical cancer who receive radiotherapy.

MATERIALS AND METHOD

This study used a double-blind, randomized clinical trial (RCT) design by comparing the treatment group that received high PUFA nutritional supplementation and the control group that received nutritional supplementation without PUFA. The study was conducted on patients with stage IIB-IIIB cervical cancer who received radiation therapy at the Radiotherapy Department of Cipto Mangunkusumo Hospital (RSCM), Jakarta. Data collection was conducted from April 2013 until a sufficient number of study samples were obtained. A total of 31 patients out of the 45 enrolled were able to complete the study: 16 patients in the treatment group and 15 in the control group.

The study population included all new patients with stage IIB-IIIB cervical cancer who received radiation therapy at the Radiotherapy Department of RSCM. Each patient diagnosed with stage IIB-IIIB cervical cancer and fulfilling the inclusion and exclusion criteria was included in the study sample. Inclusion criteria included age ≥18 years, Karnofsky index ≥60%, body mass index (BMI) ≥16 kg/m2, willingness to take oral nutritional supplements (ONS), and willingness to sign an informed consent. Exclusion criteria were patients with impaired liver function, impaired renal function, impaired carbohydrate metabolism, and fat malabsorption. Patients were considered to drop out if they did not comply with the study protocol, had delayed radiotherapy for seven consecutive days, or consumed <80% dietary supplements.

Assessment of acute radiation side effects. Acute radiation side effects were assessed weekly by the doctor. Patients were evaluated for radiotherapy-related complaints or side effects through medical history, physical examination, and laboratory tests. Evaluation results were recorded based on the Radiation Therapy Oncology Group (RTOG) grading criteria.

Nutritional supplementation. Nutritional supplementation was provided as ONS labeled A and B, containing high PUFA (omega-6: omega-3 fatty acid ratio = 1.27: 1) or no PUFA. The ONS was taken three times a day by dissolving five measuring spoons of ONS in 200 ml of warm water. ONS could be taken at any time as a meal replacement, but to improve patient compliance, the first ONS was taken in the researcher's room after the patient was registered in the Radiotherapy Department, the second was taken after radiotherapy, and the third was taken at home. The remaining ONS containers were returned to the researcher for the next day's ONS collection, and patients were asked to record all food and beverages consumed in the intake book at least three days a week, including two working days and one day off. Table 1 below details the nutritional content of ONS.

Table 1. Nutrient content of ONS in treatment groups with high PUFA and control groups with no PUFA

Nutrient content per 250 ml	High PUFA (g)	No PUFA (g)
Proteins	19	20.31
- Isoleucine	1.47	1.32
- Leucine	2.60	2.11
- Valine	1.30	1.34
Total BCAAs	5.37	3.18
Total fat	7.00	7.72
- DHA	0.49	0
- EPA	0.29	0
- Saturated fat	1.30	7.35
- Monounsaturated fat	3.00	0.27
- Polyunsaturated fat	2.20	0.09
- Cholesterol	0	0
N-3 fatty acids	0.95	0.01
N-6 fatty acids	1.27	0.05
Ratio n-3 : n-6	1: 1.27	0
Total carbohydrates (no FOS)	51	47.9
- Dietary fiber	3	0.71
- Total sugar	10	27.68
- Sucrose	3	15.36
Total energy of serving (kcal)	330	340

The data obtained were processed utilizing Statistical Program for Social Science (SPSS) software version 11.5. The measurement results in the clinical trial with randomization to the treatment group or the control group were analyzed using the Chi-Square test, Fisher Exact test, Kolmogorov Smirnov test, Independent T-test, and Mann-Whitney test. The limit of significance used was >0.05.

RESULTS

Regarding characteristics of the patients based on Table 2, there was no significant difference between the treatment group that received high PUFA nutritional supplementation and the control group that received nutritional supplementation without PUFA. Socio-demographic characteristics include age, latest education, occupation, number of biological children, contraceptive history, smoking history, or history of cancer ($p>0.05$).

Table 2. Socio-demographic characteristics of the patients according to allocation groups

	High PUFAs (n = 16)	No PUFAs (Control) (n = 15)	P-value
Age (n)			
<45 years	7	4	0.320[a]
≥45 years	9	11	
Latest education (n)			
Low	7	7	
Current	7	6	1.000[b]
High	2	2	
Occupation (n)			
Not Working	14	11	0.394[a]
Work	2	4	
Number of Biological Children (n)			
< 3	7	3	
3-5	8	9	0.269[a]
> 5	1	3	
Contraception History (n)			
Non-hormonal	3	5	
Hormonal	12	9	0.997[b]
Both	1	1	
Smoking History (n)			
Do not Smoke	16	15	-
Smoke	0	0	
History of Cancer (n)			
None	15	11	0.172[a]
Yes	1	4	

Note: [a], Chi Square Test; [b], Kolmogorov Smirnov Test

For the nutritional status of the patients based on Table 3, there was no significant difference between the treatment group receiving high PUFA nutritional supplementation and the control group receiving nutritional supplementation without PUFA. The nutritional status of the patients encompasses BMI and weight loss history (p>0.05).

Table 3. Nutritional status of the patients according to allocation group

	High PUFA (n = 16)	No PUFA (Control) (n = 15)	P-value
BMI (kg/m^2)	22.97 ± 3.92*	24.74 ± 4.93*	0.301[a]
Underweight (n)	2	-	1.000[b]
Normal weight (n)	7	8	
Overweight (n)	7	7	
History of Weight Loss			
<1 kg (n)	3	3	1.000[b]
1-5 kg (n)	6	4	
6-10 kg (n)	4	5	
>10 kg (n)	3	3	

Note: [a], Independent T-Test; [b], Chi square test; *, Mean ± SD; BMI, Body Mass Index

Additionally, Table 4 indicates that there was no significant difference between the treatment group that received nutritional supplementation high in PUFA and the control group that received nutritional supplementation without PUFA in terms of total calorie intake per day, or percentage of protein, fat, and carbohydrate intake during treatment (p>0.05). In addition, for PUFA intake and omega-6: omega-3 fatty acid intake ratio according to allocation group based on Table 4, there was a significant difference in omega-3 fatty acid intake and the ratio of omega-6: omega-3 fatty acid intake between the treatment group receiving high PUFA nutritional supplementation and the control group receiving nutritional supplementation without PUFA (p<0.05). However, there was no significant difference in omega-6 fatty acid intake between the two groups (p>0.05).

Table 4. Total calorie intake per day, percentage of macronutrient intake, PUFA intake, and omega-6: omega-3 fatty acid intake ratio according to allocation group

Variable	Group		P-value
	High PUFA (n = 16)	No PUFA (Control) (n = 15)	
Total Calories per day (Kkal)	1821.88 (1499.86-2294.39)^	1709.49 (1471.13-2460.40)^	0.216[a]
Protein (%)	19.29 ± 1.71*	19.78 ± 1.53*	0.412[b]
Fat (%)	22.69 ± 2.87*	24.53 ± 3.86*	0.140[b]
Carbohydrates (%)	56.02 ± 2.51)*	55.73 ± 3.68*	0.051[b]
PUFA intake:			
Intake omega-6 PUFA (g)	2.07 (0.65-7.68)^	2.18 (0.68-3.53)^	0.520[a]
Intake omega-3 PUFA (g)	2.72 ± 0.31*	0.51 ± 0.16*	<0.001[b]
Intake Ratio n-6 : n-3 PUFA	0.83 (0.33-2.53)^	3.60 (1.94-9.58)^	<0.001[a]

Note: [a], Mann Whitney test; [b], Independent T-Test; *, Mean ± SD; ^, Median (minimum-maximum)

The effect of high PUFA nutritional supplement on acute radiation side effects

Acute radiation side effects can be in the form of general or localized complaints. A common complaint often experienced by patients with cancer is a lack of appetite. Therefore, general complaints obtained from direct medical history can be measured through changes in body weight. The following are weight measurements taken weekly during radiotherapy (Figure 1).

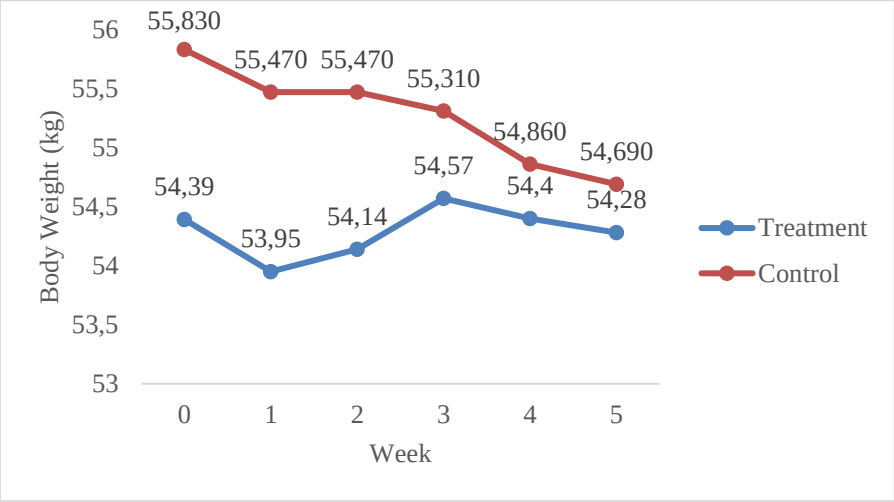

Figure 1. The body weight of the patients during radiotherapy according to the allocation group
Note: Week 0 is the body weight before PUFA feeding.

As Figure 1 depicted, the body weight of the treatment group that received high PUFA nutritional supplementation was relatively more stable, while the control group that received nutritional supplementation without PUFA decreased (p=0.539), but the Δ weight loss was not significantly different between the groups (p=0.149). Furthermore, Table 5 details the acute radiation effects in both groups assessed at the end of the study using the Radiation Therapy Oncology Group (RTOG) scoring criteria. The treatment and control groups exhibited no significant difference in acute radiation side effects.

Table 5. Acute radiation side effects according to allocation group

Adverse Effects Acute Radiation	High PUFA (n =16)	No PUFA (Control) (n = 15)	P-value
Skin			
Degree 0	0 (0.0)	1 (6.7)	0.562[a]
Degree 1	12 (75.0)	10 (66.7)	
Degree 2	4 (25.0)	4 (26.7)	
Degree 3	0 (0.0)	0 (0.0)	
Degree 4	0 (0.0)	0 (0.0)	
Gastrointestinallower			
Degree 0	6 (37.5)	7 (46.7)	0.800[a]
Degree 1	8 (50.0)	7 (46.7)	
Degree 2	2 (12.5)	1 (6.7)	
Degree 3	0 (0.0)	0 (0.0)	
Degree 4	0 (0.0)	0 (0.0)	
Genitourinary			
Degree 0	9 (56.2)	9 (60.0)	0.248[a]
Degree 1	7 (43.8)	4 (26.7)	
Degree 2	0 (0.0)	2 (13.3)	
Degree 3	0 (0.0)	0 (0.0)	
Degree 4	0 (0.0)	0 (0.0)	
Hemoglobin			
Degree 0	8 (50.0)	8 (53.3)	1.000[b]
Degree 1	8 (50.0)	7 (46.7)	
Degree 2	0 (0.0)	0 (0.0)	
Degree 3	0 (0.0)	0 (0.0)	
Degree 4	0 (0.0)	0 (0.0)	
Leukocytes			
Degree 0	13 (81.2)	14 (93.3)	0.600[b]
Degree 1	3 (18.8)	1 (6.7)	
Degree 2	0 (0.0)	0 (0.0)	
Degree 3	0 (0.0)	0 (0.0)	
Degree 4	0 (0.0)	0 (0.0)	
Platelets			
Degree 0	15 (93.8)	15 (100.0)	1.000[b]
Degree 1	0 (0.0)	0 (0.0)	
Degree 2	1 (6.2)	0 (0.0)	
Degree 3	0 (0.0)	0 (0.0)	
Degree 4	0 (0.0)	0 (0.0)	

Note: [a] Chi-Square Test; [b], Fisher Exact Test

DISCUSSION

Characteristics of patients based on socio-demographics. Based on the results of socio-demographic research, the patients enrolled in this study did not display a significant difference in characteristics between the treatment group that received high PUFA nutritional supplementation and the control group that received nutritional supplementation without PUFA. The age distribution of the patients in this study ranged from 28-80 years, with 64% aged ≥45 years. Twenty-one patients had a history of hormonal contraception, but it was not known how long the use of hormonal contraception had been. In addition, >70% of the patients were passive smokers. This study aligns with the research of [13] who uncovered the highest incidence of cervical cancer in the age group ≥45 years, namely 46-55 years, with a history of hormonal contraception, namely oral/pills, injections, and implants, and being a passive smoker.[13]

Moreover, increasing age can make a person more susceptible to cervical cancer due to behavioral factors, diet, and hormonal changes that can increase or decrease the effect of carcinogens.[14,15] Long-term use of hormonal contraceptives can also disrupt the balance of the hormone estrogen in the body, causing abnormal changes in cells.[16] In addition, active or passive smoking can reduce the immune system because

nicotine content in cigarette smoke can damage cervical cell DNA and contribute to the development of cervical cancer. A decreased immune system will accelerate the growth of HPV, which causes cervical precancerous lesions. However, the relationship between exposure to cigarette smoke and the amount of nicotine inhaled that can cause cervical cancer is not yet known for certain.[17]

The distribution of patient occupations and education in this study revealed that 25 patients (80%) were housemakers who did not work outside the home, with 14 patients (45%) with low education or up to elementary school. The results of this study are consistent with research by [18] showing that most patients with cervical cancer work as homemakers (51.35%) with an elementary education level (48.6%). Related to that, employment and education can affect the incidence of cervical cancer. The type of work or economic status affects a person's ability to seek treatment at a health center when experiencing signs and symptoms or for cervical cancer screening.[18] The level of education also affects a person's way of thinking so that the higher a person's level of education, the easier it is to seek, obtain, and perhaps understand information.[14,18]

The results of research on the distribution of the number of biological children demonstrated that 21 patients (68%) had ≥3 biological children. This study agrees with research conducted by [14], indicating that one of the high risks for cervical cancer is a history of multiparity. Parity is one of the risk factors for cervical cancer, as the number of pregnancies and childbirth processes can cause trauma or a decrease in the immune system, increasing the risk of HPV infection. In addition, education can also affect decisions on the number of children. The higher the level of education, the ability to think more rationally, such as the ideal number of children is two.[14]

The distribution of the cancer history in this study showed that 26 patients (84%) did not have a history of cancer themselves or in their close family. The results of this study are in line with the research of Ananti and Sari (2020), who found that 93.12% of patients with cervical cancer have no family history of cancer.[19] This is due to the etiology of cervical cancer, namely that 99.7% of cervical cancer is caused by HPV associated with sexual lifestyle. However, although HPV plays a role in the development of cervical cancer, it is not the only cause of cervical cancer.[20] Cervical cancer can be caused by numerous factors, such as lifestyle, diet, and hygiene patterns that can trigger HPV infection.[21]

Characteristics of patients based on nutritional status. The characteristics of nutritional status, namely body mass index (BMI) and weight loss history during illness or the last three months, exhibited no significant difference between the treatment group that received high PUFA nutritional supplementation and the control group that received nutritional supplementation without PUFA. The results showed that as many as 8 patients in the control group had a normal BMI, while 7 patients in the treatment group and 8 patients in the control group had lost weight >5 kg in the last three months. This study corroborates with the research of [22], which revealed that 2.5 gr of omega-3 PUFAs per day are effective in maintaining nutritional status and skeletal muscle mass and reducing chemoradiotherapy symptoms in women with cervical cancer.[22]

Nutrition is one of the most important factors in the management of cancer treatment.[23] Patients with cancer often experience nutritional problems due to side effects of therapy, such as anorexia, changes in taste threshold, weight loss, anemia, and metabolic disorders.[24] Cancer can cause changes in protein, fat, and carbohydrate metabolism caused by lack of energy intake and increased energy use.[8,23] Weight loss in patients with cancer can be caused by several factors, including metabolic disorders due to the cancer itself and side effects of therapy, such as loss of appetite.[24] A person's weight loss can be followed by a decrease in BMI, which is due to a decrease in fat tissue and skeletal muscle mass.[8]

Meanwhile, malnutrition is a state of decreased nutrition in patients with cancer that can adversely affect the results of therapy and can increase morbidity and mortality compared to patients with good nutritional status.[24,25] The prevalence of malnutrition in patients with cancer varies depending on the type of tumor, organs involved, stage of disease, response to therapy, and history of comorbidities. The nutritional status of patients with cancer is determined based on anamnesis, physical examination, and laboratory tests. The use of anthropometry is one of the main principles in assessing nutritional status, which includes measuring height and weighing body weight to determine BMI.[24] Nutritional status data seen through BMI parameters are needed to support the provision of therapy and determine a better prognosis.[25]

Specifically, recent weight change is an indicator of nutritional deficits and determines a person's nutritional status, whether it is normal, mild, or severe malnutrition. Weight loss ≥5% in three months or ≥10% in the previous six months indicates malnutrition.[26] Based on the results of the study, most of the patients did not know their weight before illness. Weight loss data in this study was calculated based on body weight at the time of diagnosis of cervical cancer compared to body weight when the patient was admitted to the Radiotherapy Department. If the body weight before illness is around 60 kg and it is estimated that there is

a weight loss of 5% or more, it can be interpreted that most patients came in a condition at risk of malnutrition or malnutrition.

The causes of malnutrition in patients with cancer are multifactorial, namely decreased nutrient intake and metabolic changes in the body.[7,27] Metabolic changes in patients with cancer include changes in carbohydrate metabolism, including hyperinsulinism and insulin resistance. Changes in protein metabolism in cancer are increased protein catabolism and gluconeogenesis from amino acids in the liver, leading to loss of muscle mass. Changes in fat metabolism in patients with cancer include decreased lipogenesis, decreased lipoprotein lipase (LPL) activity, and increased lipolysis.[7] Metabolic changes affect the immune system, so efforts are needed for prevention through improved nutrition, such as eating fruits, vegetables, and antioxidants.[27]

Total calorie intake per day and percentage of macronutrient intake during treatment. During the treatment, the total calorie intake per day between the treatment group that received nutritional supplementation high in PUFA and the control group that received nutritional supplementation without PUFA was not significantly different, nor was the percentage intake of protein, fat, and carbohydrates. Based on the results of the study, the total calorie requirement calculated using the rule of thumb, which is around 30-35 kcal/kgBB/day with an average BW of the treatment group of 54 ± 9.3 kg and the control group of 55.8 ± 12.6 kg, means that the total calorie requirement has been met. The results of this study corroborate with [8] research, which showed an average energy consumption of 1307.39 ± 548.58 kcal with a percentage of 78.52%, which means that energy adequacy is adequate because it meets ≥70% of the needs.[8]

Furthermore, factors that can cause a decrease in energy and macronutrient intake in patients with cancer include increased catabolism, medical therapy that can reduce appetites, such as the effects of anesthesia due to surgery, chemotherapy, and radiation, as well as lack of motivation and support from within oneself and the environment. According to the nutritional management of patients with cancer in the European Society for Clinical Nutrition and Metabolism (ESPEN) Guideline, energy and macronutrient intake only fulfilled <60% of the total needs of patients with cancer in a day. [(8)] Energy and macronutrient intake in patients with cancer must be considered carefully so that the nutritional status of patients remains within normal limits.[7]

The energy intake needs of patients with cancer are 30 kcal/kgBB/day, protein is 1.5 gr/kgBB/day or equivalent to 20% of calorie needs, fat is 35% of calorie needs, and carbohydrates are 45% of total calorie needs.[8] Some studies have shown that some patients with advanced-stage cancer experience an increase in BMR (Basal Metabolic Rate) at rest and during activity.[27] Energy requirements increase by 100-300 kcal/day, which can lead to a decrease in body fat of about 0.5-1 kg/month or muscle mass of about 1-2.3 kg/month.[9]

Protein is one of the important components of the human body that plays a role in repairing damaged cells and tissues in diseases including cancer. Protein can be obtained from animal and vegetable sources.[8] The average protein intake in patients with cancer with cachexia is around 0.7-1 gr/kgBB/day.[28] Protein deficits in patients with cancer are 0.3-0.5 gr/kgBB/day, so protein intake must be increased by 50% or 1-1.5 gr/kgBB/day.[9] Adequate protein intake can affect the nutritional status of patients. The better and more diverse the intake of food sources of protein, the longer the impact on nutritional status.[8]

In addition, a high intake of fat and carbohydrates can also improve a person's nutritional status. Fat and carbohydrate intake are factors that significantly affect nutritional status, especially in older people.[8] Fat can be given 30-50% of total calorie needs.[7] Normal metabolism of carbohydrates, namely aerobic glycolysis, produces 36 to 38 ATP, but in cancer with cachexia, anaerobic glycolysis produces 2 ATP, which distributes glucose for tumor growth.[27] Glucose intake can be replaced with fat in parenteral nutrition to avoid the risk of infection-related hyperglycemia that often occurs in patients with cancer.[9]

PUFA intake and omega-6: omega-3 fatty acid intake ratio during treatment. Based on the results of the study of PUFA intake and the ratio of omega-6: omega-3 fatty acid intake during the treatment, there were significant differences in omega-3 fatty acid intake and the ratio of omega-6: omega-3 fatty acid intake between the treatment group that received nutritional supplementation high in PUFA and the control group that received nutritional supplementation without PUFA. Omega-6 linoleic acid intake and omega-6: omega-3 ratio play a role in the development of various diseases, including coronary heart disease, autoimmune diseases, and cancer. Blood levels of omega-6 and omega-3 fatty acids are determined by endogenous metabolism and dietary intake, so a balanced dietary intake is important for health and disease prevention.[29]

The recommended intake for PUFA is based on the body's regulation. The Dietary Guidelines for Americans recommends about 230 gr/week, corresponding to 250 mg/day of EPA and DHA or the equivalent of consuming fish twice a week. According to WHO, total PUFA consumption in adults is about 6-11% of total

energy requirements.[30] The ratio of omega-6 and omega-3 plays a role in the development of obesity through mechanisms of gene expression in adipogenesis, lipid homeostasis, Brain-Gut-Adipose tissue axis, and inflammation. Omega-6 and omega-3 PUFA can also act as transcription factors to regulate the expression of genes involved in pre-adipocyte differentiation.[31]

Pre-adipocyte differentiation begins when arachidonic acid (AA) metabolites play a role in the differentiation of terminal pre-adipocytes into mature adipocytes, which omega-3 fatty acids can inhibit. Omega-6 fatty acids increase cellular triglyceride content by increasing membrane permeability, whereas omega-3 fatty acids reduce fat accumulation in adipose tissue by inhibiting lipogenic enzymes and increasing β-oxidase.[32] Omega-6 and omega-3 fatty acids are specifically metabolized to prostaglandins, thromboxane, and leukotrienes. Prostaglandin E2 (PGE2) from AA causes differentiation and proliferation of adipose tissue and prevents browning of white adipose tissue (WAT), which is good fat tissue because it increases thermogenesis and the burning of fat through heat release.[33]

The mechanism by which omega-6 and omega-3 affect body fat is through the Brain-Gut-Adipose tissue axis, where omega-6 increases the production of endocannabinoids, which control appetite and energy balance. Meanwhile, omega-3 PUFAs can decrease endocannabinoid production and related receptor sensitivity. Omega-6 and omega-3 may influence the leptin signaling pathway to regulate body weight by affecting appetite and energy expenditure. Omega-6 may increase leptin production, while omega-3 decreases leptin production and leptin receptors. In addition, omega-6 and omega-3 PUFAs can regulate the expression and secretion of adiponectin, which suppresses several obesity-related pathological processes. Omega-6 may decrease the production of adiponectin, while omega-3 may increase adiponectin production.[31]

The effect of high PUFA nutritional supplements on acute radiation side effects. One of the side effects of acute radiation is weight loss. This study measured body weight every week during radiation. Based on statistical results, there was no significant difference in weight loss between the treatment group that received high PUFA nutritional supplementation and the control group that received nutritional supplementation without PUFA. However, Figure 1 illustrates that the body weight of the treatment group was relatively more stable, while that of the control group decreased. The results of this study are in harmony with the research of [5], which showed that during treatment, all research subjects experienced weight loss without the provision of high PUFA nutritional supplementation. Weight loss is caused by a decrease in fat mass (FM) and/or fat-free mass (FFM).[5]

Primary treatment of cervical cancer requires a combination of therapies, such as surgery, radiotherapy, and chemotherapy.[25,34,35,36.] Radiotherapy is the most common treatment given to patients with cancer by using high doses of radiation to kill cancer cells and shrink tumor size.[34] Radiotherapy treatment in patients with advanced cervical cancer consists of a combination of external beam radiotherapy (EBRT) and brachytherapy (BT). Radiotherapy can cause physical, psychological, and social changes, such as the effects of radiation on the pelvis can be nausea, vomiting, changes in bowel function, lactose intolerance, fatigue, and loss of appetite.[5] Short-term effects of radiotherapy will be experienced immediately by patients, while long-term effects can occur in the weeks, months, or years after radiotherapy.[5,34]

Some of the effects of radiotherapy can be reduced through physical exercise, which helps patients increase their appetite and prevent muscle mass loss.[5] However, many patients are unable to increase physical activity due to fatigue, nausea, vomiting, or diarrhea.[8] The side effects and symptoms caused by radiotherapy can worsen the nutritional status of patients with cancer. The nutritional status of patients will worsen in patients with advanced-stage cancer, in older people, in those with a history of other chronic diseases, and in those with a history of smoking, which can affect the risk of radiotherapy toxicity for patients with cervical cancer. The decline in nutritional status can be worse because patients have fewer nutritional reserves and are unable to compensate for decreased energy intake or energy absorption.[5]

Based on the results of the study, the majority of patients experienced symptoms of nausea, vomiting, and diarrhea, but the effects of radiotherapy might vary from patient to patient. Some patients stated that they did not experience nausea, and their appetite was quite good, while others stated that they experienced nausea and had decreased appetite for days. Post-radiotherapy nausea and vomiting can also be caused by radiation enteritis, while diarrhea can be caused by malabsorption. The effects of radiotherapy cause weight loss, which can affect the nutritional status of the patient. Nutritional education and modification are important to prevent a decrease in intake that can worsen the patient's condition.[5]

Nutritional supplements high in PUFA, which are essential fats, are crucial.[10,37] Omega-3 PUFA plays a role in inhibiting cell growth and inducing apoptosis in various types of cancer cells, while omega-6 PUFA has a pro-inflammatory effect. Giving omega-3 together with chemotherapy drugs can increase the radiosensitivity of tumors.[38] In addition, PUFA also plays a role in maintaining dietary disorders.[(11)] The results

of this study indicate that supplementing high PUFA nutrition in patients with cervical cancer can help to maintain body weight.

Acute radiation side effects can also affect the skin, lower gastrointestinal tract, genitourinary tract, hemoglobin, leukocytes, and platelets. Based on statistical results, there was no significant difference in the side effects of acute radiation in the treatment group that received high PUFA nutritional supplementation and the control group that received nutritional supplementation without PUFA. The results of research conducted by [39] showed that in patients with cervical cancer, hemoglobin decreased by 4.07%, leukocytes decreased by 38.3%, and platelets decreased by 22.53%.[39] Research conducted by [40] demonstrated that there was a risk of severe urinary side effects of 0.25% per year for at least 25 years after radiotherapy.[40]

Radiation disrupts the hemopoietic system and reduces the total number of blood cells. Hemoglobin is a protein that binds and carries oxygen. Leukocytes protect the body against invasion by foreign bodies, such as bacteria and viruses. Platelets function in the blood clotting mechanism. Leukocyte and platelet counts display significant changes after receiving a radiation dose, while erythrocytes and hemoglobin are resistant to radiation. A decrease in leucocyte production can lead to a weakened immune system, making radiation therapy patients more susceptible to diseases caused by infections, bacteria, or viruses. Decreased platelet production can cause patients to bleed easily because the clotting system is disrupted.[39]

In addition, radiation-induced structural tissue damage proceeds according to a linear threshold. Damage to the vascular basement membrane can lead to occlusion, thrombosis, and neovascularization. Tissue atrophy and shrinkage are caused by increased fibroblast proliferation. All these changes can cause significant damage to the urinary tract. Bladder damage and loss of capacity can lead to significant urinary tract symptoms. Replacement of the spongiosum body by fibrosis and obstruction of the urethral lumen are principal factors that increase the rate of urethral strictures after radiotherapy.[40]

CONCLUSION

The results revealed that PUFA supplementation (ratio of omega-6 fatty acids: omega-3 = 1.27: 1) could maintain the nutritional status of patients with cervical cancer by maintaining a stable body weight, although side effects were not influenced.

ETHICAL CONSIDERATIONS

The study received approval from the Health Research Ethics Committee Faculty of Medicine Universitas Indonesia Cipto Mangunkusumo Hospital with no: 176/H2.F1/ETIK/2013.

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CONFLICT OF INTEREST

The author does not have any conflict of interest.

AUTHOR CONTRIBUTIONS

SW conceived the experiment, planned the experiment, experimented, processed the experimental data, and analyzed and drafted the manuscript.

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