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Submission date: 20-Mar-2024 02:37PM (UTC+0700)
Submission ID: 2325592807
File name: Jurnal_dr._Sri_Wuryanti_english.docx (57.17K)
Word count: 6802
Character count: 39474

Effect of Nutritional Supplementation High in Polyunsaturated Fatty Acids (PUFA) on the Nutritional Status of Advanced Cervical Cancer Patients Receiving Radiotherapy

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ABSTRACT

BACKGROUND
In 30-90% of cancer patients, weight loss is caused by inadequate intake, changes in metabolism, and inflammatory and humoral responses between the host and tumor. Longitudinal studies have shown that cancer patients who experience weight loss have a worse prognosis than those with stable weight. This change is thought to affect therapeutic response. Polyunsaturated Fatty Acids (PUFA) omega-6 : omega-3 intake ratio of about 1-2 : 1 may fight cancer growth. Several publications reported that PUFA omega-3 has pro-apoptotic, anti-inflammatory, anti-proliferative and anti-angiogenic effects. This study aims to determine the effect of high PUFA nutritional supplementation on the nutritional status of advanced cervical cancer patients who receive radiotherapy.

METHODS
This study was a double-blind Randomised Clinical Trial on advanced cervical cancer patients at the Radiotherapy Department, Cipto Mangunkusumo Hospital (RSCM), Jakarta, from April 2013 to April 2014. The study subjects were taken consecutively, through randomization divided into two groups, namely the treatment and control groups. During radiation, the subjects received nutritional supplementation containing isocaloric and isoproteins with a ratio of omega-6 : omega-3 fatty acids = 1.27 : 1 and control. During treatment, weekly evaluations were conducted, including body weight and acute radiation side effects.

RESULTS
A total of 31 subjects out of 45 subjects were able to complete the study, with 16 subjects in the treatment group and 15 subjects in the control group. Before treatment, socio-demographic status, omega-6 and omega-3 fatty acid intake patterns, nutritional and clinical status were not significantly different. The body weight of the treatment group that received high PUFA nutritional supplementation with a ratio of omega-6 : omega-3 fatty acids = 1.27 : 1 was relatively more stable, while the control group that received nutritional supplementation without PUFA decreased (p = 0.539), but the Δ weight loss in each group was not significantly different (p = 0.149).

CONCLUSIONS
PUFA supplementation can maintain the nutritional status of cervical cancer patients 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 cases with a total death of 341,831 people. The incidence of cervical cancer in Indonesia in 2020 according to WHO is 36,633 cases or constitutes 9.2% of all cancer cases and ranks second after breast cancer.[(1)] Cervical cancer occurs in the cervix 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 cervical cancer patients 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 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 cancer patients 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, such as drugs used during chemotherapy cannot work optimally.[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]

Polyunsaturated fatty acids (PUFA) consist of omega 3 or alpha-linolenic acid (ALA), which consists of eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), while omega 6 or linolenic acid (LA) includes arachidonic acid (AA). Omega-3 and omega-6 are essential fatty acids that cannot be produced by the body 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, PUFAs play an important 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 shown that PUFAs have anticancer properties. Consumption of omega-3 can suppress inflammation, stimulate apoptosis, inhibit tumor metastasis and proliferation, and upregulate gene expression of antioxidant enzymes. Consumption of omega-6 has a carcinogenic effect that correlates with an increase in the eicosanoid ratio.[12] This study aims to determine the effect of high PUFA nutritional supplementation on the nutritional status of advanced cervical cancer patients who receive radiotherapy.

METHODS

Research design

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 stage IIB-IIIB cervical cancer patients 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.

Study Population and Sample

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

Assessment of acute radiation side effects

Acute radiation side effects are assessed by the doctor every week. 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 measurement

Nutritional supplementation was provided as oral nutritional supplements (ONS) labeled A and B, each containing high PUFA (omega-6 : omega-3 fatty acid ratio = 1.27 : 1) and no PUFA. The ONS is 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 ONS was taken after radiotherapy, and the third ONS 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.

Statistical analysis

The data obtained were processed using Statistical Program for Social Science (SPSS) software version 11.5. The measurement results in the clinical trial with randomization in the treatment group and 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

Characteristics of research subjects based on socio-demographics

Table 1 shows the socio-demographic characteristics of research subjects associated with risk factors or suspected causes of cervical cancer.

Table 1 Distribution of research subjects based on socio-demographic characteristics

	Treatment Group (n = 16)	Control Group (n = 15)	P value
Age (n)			
<45 years	7	4	0,320[a]
≥45 years	9	11	
Last Education (n)			
Low	7	7	
Currently	7	6	1,000[b]
High	2	2	
Occupation (n)			
Doesn't Work	14	11	0,394[a]
Work	2	4	
Number of Biological Children (n)			
< 3 people	7	3	
3-5 people	8	9	0,269[a]
> 5 people	1	3	
Contraception History (n)			
Non Hormonal	3	5	
Hormonal	12	9	0,997[b]
Both of them	1	1	
Smoking History (n)			
Do not Smoke	16	15	-
Smoke	0	0	
History of Cancer (n)			
There isn't any	15	11	0,172[a]
There is	1	4	

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

Based on Table 1, 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 in age, latest education, occupation, number of biological children, contraceptive history, smoking history, or history of cancer (p>0.05).

Characteristics of research subjects based on nutritional status

Table 2 shows the characteristics of nutritional status based on BMI and history of weight loss during illness or the last 3 months.

Table 2 Characteristics of nutritional status of research subjects

	Treatment Group (n = 16)	Control Group (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]
Normoweight (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

Based on Table 2, there was no significant difference between the treatment group receiving high PUFA nutritional supplementation and the control group receiving nutritional supplementation without PUFA in BMI and weight loss history ($p>0.05$).

Total calorie intake per day and percentage of macronutrient intake during treatment

Table 3 shows the total calorie intake per day and the percentage intake of protein, fat, and carbohydrate.

Table 3 Total calorie intake per day and percentage of macronutrient intake during treatment

Variable	Group		P value
	Treatment (n = 16)	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]
Carbohydates (%)	56,02 ± 2,51)*	55,73 ± 3,68*	0,051[b]

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

Based on Table 3, 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 total calories per day, percentage of protein, fat, and carbohydrate ($p>0.05$).

PUFA intake and omega-6 fatty acid intake ratio: omega-3 during treatment

Table 4 shows the results of the analysis of PUFA intake and the intake ratio of omega-6 and omega-3 fatty acids.

Table 4 PUFA intake and omega-6 fatty acid intake ratio: omega-3 during treatment

Variable	Group		P value
	Treatment (n = 16)	Control (n = 15)	
Intake AL omega-6 (g)	2,07 (0,65-7,68)^	2,18 (0,68-3,53)^	0,520[a]
Intake AL omega-3 (g)	2,72 ± 0,31*	0,51 ± 0,16*	<0,001[b]
Intake Rasio AL n-6 : n-3	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); AL: fatty acid

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 ($p<0.05$) while in omega-6 fatty acid intake there was no significant difference between the treatment group receiving high PUFA nutritional supplementation and the control group receiving nutritional supplementation without PUFA ($p>0.05$).

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 cancer patients 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).

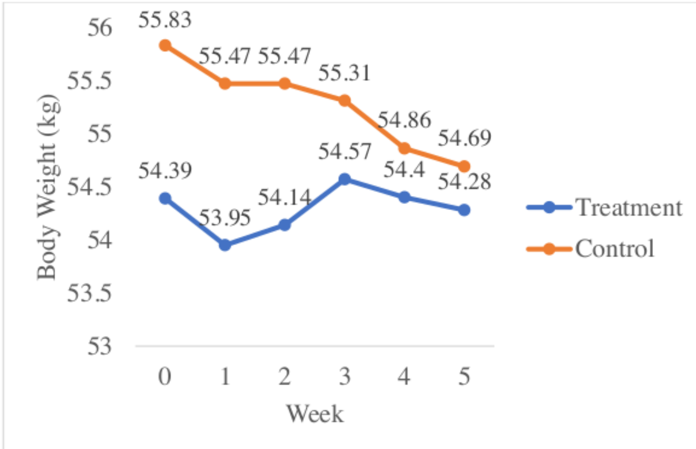

Figure 1. Monitoring the weight of the research subjects during treatment

Based on Figure 1, 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 in each group was not significantly different (p=0.149).

The following is the effect of high PUFA nutritional supplementation on acute radiation effects in both groups assessed at the end of the study using the Radiation Therapy Oncology Group (RTOG) scoring criteria.

Table 5 Effect of high PUFA nutritional supplementation on acute radiation side effects

Adverse Effects Acute Radiation	Treatment Group (n =16)	Control Group (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)	
Gastrointestinal lower			
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

The treatment and control groups showed no significant difference in acute radiation side effects.

DISCUSSION

Characteristics of research subjects based on socio-demographics

Based on the results of socio-demographic research, the research subjects in this study did not have a significant difference 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 subjects in this study ranged from 28-80 years with 64% aged ≥45 years, 21 subjects had a history of hormonal contraception, but it was not known how long the use of hormonal contraception was. In addition, >70% of the subjects were passive smokers. This study is in line with the research of Ningsih, Pramono, Nurdianti (2017) found that the highest incidence of cervical cancer in the age group ≥45 years, namely 46-55 years, has a history of hormonal contraception, namely oral / pills, injections, and implants, and is a passive smoker.(13)

The increasing age a person can be 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 disrupt the balance of the hormone estrogen in the body, causing abnormal changes in normal cells.(16) Active or passive smoking can reduce the immune system due to nicotine content in cigarette smoke which 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 subject occupations in this study, namely as many as 25 subjects (80%) were housewives who did not work with 14 subjects (45%) with low education or up to elementary school. The results of this study are in line with research by Wulandari (2016) which shows that most cervical cancer patients work as housewives (51.35%) with an elementary education level (48.6%). 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 affects a person's way of thinking, so that the higher a person's level of education, the easier it is to obtain information.(14,18)

The results of research on the distribution of the number of biological children showed that 21 subjects (68%) had ≥3 biological children. This study is in line with research conducted by Rahmawati (2017) which shows one of the high risks of cervical cancer with a history of mothers who have multiparity. Parity is one of the risk factors for cervical cancer, so 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 also affects 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 subject's cancer history in this study, namely as many as 26 subjects (84%) did not have a history of cancer, as well as in a family of one blood relationship. The results of this study are in line with the research of Ananti and Sari (2020) found that 93.12% of patients with cervical cancer have no family history of cancer.(19) This is to the etiology of cervical cancer, namely 99.7% of cervical cancer is caused by HPV associated with sexual lifestyle. HPV plays a role in the development of cervical cancer but is not the only cause of cervical cancer.(20) Cervical cancer can be caused by various factors, such as lifestyle, diet, and hygiene patterns that can trigger HPV infection.(21)

Characteristics of research subjects 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 showed that 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. The results showed that as many as 8 subjects of the control group had a normal body mass index, 7 subjects of the treatment group and 8 subjects of the control group had lost weight >5 kg in the last 3 months. This study is in line with the research of Aredes et al., 2019 which shows that 2.5 grams of omega-3 supplements 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] Cancer patients 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 cancer patients 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 body mass index, which is due to a decrease in fat tissue and skeletal muscle mass.[8]

Malnutrition is a state of decreased nutrition in cancer patients that will 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 cancer patients varies depending on the type of tumor, organs involved, stage of disease, response to therapy, and history of comorbidities. The nutritional status of cancer patients 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 body mass index.[24] Nutritional status data seen through body mass index parameters are needed to support the provision of therapy and determine a better prognosis.[25]

Recent weight change is an indicator of nutritional deficits and determines a person's nutritional status whether it is normal, mild to severe malnutrition. Weight loss ≥5% in 3 months or ≥10% in the previous 6 months indicates malnutrition.[26] Based on the results of the study, most of the research subjects 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 to have a weight loss of 5% or more, it can be interpreted that most patients come in a condition at risk of malnutrition or malnutrition.

The causes of malnutrition in cancer patients are multifactorial, namely decreased nutrient intake and metabolic changes in the body.[7,27] Metabolic changes in cancer patients include changes in carbohydrate metabolism, namely hyperinsulinism and insulin resistance. Changes in protein metabolism in cancer are decreased protein catabolism and gluconeogenesis from amino acids in the liver, leading to loss of muscle mass. Changes in fat metabolism in cancer patients 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, as well as 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, which means that the total calorie requirement has been met. The results of this study are in line with Darmawan and Adriani's (2019) 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]

Factors that can cause a decrease in energy and macronutrient intake in cancer patients 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 cancer patients written in The European Society for Clinical Nutrition and Metabolism (ESPEN) Guideline, states that energy and macronutrient intake only fulfilled <60% of the total needs of cancer patients in a day.[8] Energy and macronutrient intake in cancer patients must be considered carefully so that the nutritional status of patients remains within normal limits.[7]

The energy intake needs of cancer patients are 30 kcal/kgBB/day, protein by 1.5 grams/kgBB/day or equivalent to 20% of calorie needs, fat by 35% of calorie needs, and carbohydrates by 45% of total calorie needs.[8] Some cancer studies show that some cancer patients with advanced stages 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 in cancer is one of the important components of the human body that plays a role in repairing damaged cells and tissues. Protein intake can be obtained from animal and vegetable sources.[8] The average protein intake in cancer patients with cachexia is around 0.7-1 grams / kgBB / day.[28] Protein deficits in cancer patients are 0.3-0.5 grams / kgBB / day, so protein intake must be increased by 50% or 1-1.5 grams / 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 the elderly.[8] Fat intake 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 tumour growth.[27] Glucose intake can be replaced with fat in parenteral nutrition to avoid the risk of infection-related hyperglycemia that often occurs in cancer patients.[9]

PUFA intake and omega-6 fatty acid intake ratio: omega-3 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 PUFAs is based on the body's regulation. The Dietary Guideline for Americans recommends about 230 grams/week, corresponding to 250 milligrams/day of EPA and DHA or the equivalent of consuming fish twice a week. According to WHO, 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 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 can be inhibited by omega-3 fatty acids. 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, thromboxanes, 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 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 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]

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 shows that the body weight of the treatment group is relatively more stable, while the control group has decreased. The results of this study are in line with the research of Novitasari et al., 2016 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 cancer patients by using high doses of radiation to kill cancer cells and shrink tumor size.[34] Radiotherapy treatment in advanced cervical cancer patients 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 cancer patients. The nutritional status of patients will worsen in cancer patients with advanced stages, elderly, have a history of other chronic diseases, and have a history of smoking which can affect the risk of radiotherapy toxicity for cervical cancer patients. The decline in nutritional status can be worse because it has fewer nutritional reserves and is unable to compensate for decreased energy intake or energy absorption.[5]

Based on the results of the study, the majority of subjects experienced symptoms of nausea, vomiting, and diarrhea, but the effects of radiotherapy may vary from subject to subject. Some subjects stated that they did not experience nausea and their appetite was quite good, while others stated that they experienced nausea and 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 PUFAs, also known as polyunsaturated fats, contain essential fats, such as omega-3 and omega-6 which are very important for the body but cannot be produced by the body.[10,37] Omega-3 plays a role in inhibiting cell growth and inducing apoptosis in various types of cancer cells while omega-6 has a pro-inflammatory effect. Giving omega-3 together with chemotherapy drugs can increase the radiosensitivity of tumors.[38] In addition, PUFAs also play a role in maintaining dietary disorders.[11] The results of this study indicate that supplementing high PUFA nutrition in cervical cancer patients can relatively maintain body weight.

Acute radiation side effects can also affect the skin, lower gastrointestinal, genitourinary, hemoglobin, leukocytes, and platelets. Based on statistical results, there is no significant difference in the side effects of acute radiation on 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 Nisa et al., 2014 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 Liberman et al., 2014 showed 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. Haemoglobin 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 show 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 important factors that increase the rate of urethral strictures after radiotherapy.[40]

CONCLUSIONS

The results showed that PUFA supplementation (ratio of omega-6 fatty acids: omega-3 = 1.27: 1) can maintain the nutritional status of cervical cancer patients by maintaining a stable body weight, although side effects did not make a significant difference.

ETHICAL CONSIDERATIONS

The study has received approval from the ethical committee…

ACKNOWLEDGEMENTS

I would like to thank Prof. Dr. dr. Adrijono, SpOG(K), Prof. Dr. dr. R. Susworo, SpRad. SpOnk.Rad, Dr. dr. Fiastuti Witjaksono MSc, MS, SpGK, Prof. Dr. dr. Saptawati Bardosono, MSc (Alm.), and PT KALBE.

CONFLICT OF INTEREST

The authors do not have any conflict of interest.

AUTHOR CONTRIBUTIONS

SW conceived the experiment, planned the experiment, conducted the experiment, processed the experimental data, analyzed and drafted the manuscript with input from all authors.

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