Original Article

Nutritional Intervention With Fish Oil Provides a Benefit Over Standard of Care for Weight and Skeletal Muscle Mass in Patients With Nonsmall Cell Lung Cancer Receiving Chemotherapy

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BACKGROUND: Involuntary weight loss is a major contributor to mortality and morbidity in patients with advanced cancer. Nutritional intervention with fish oil (FO)-derived eicosapentaenoic acid (EPA) may prevent deterioration of body composition. This study compared intervention with FO with standard of care (SOC; no intervention) with regard to weight, skeletal muscle, and adipose tissue in newly referred patients with nonsmall cell lung cancer from the time of initiation to completion of first-line chemotherapy. **METHODS:** Forty patients completed the study; there were 16 in the FO group (dose of 2.2 g of EPA/day) and 24 patients in the SOC group. Skeletal muscle and adipose tissue were measured using computed tomography images. Blood was collected and weight was recorded at baseline and throughout chemotherapy. **RESULTS:** Patients in the SOC group experienced an average weight loss of 2.3 ± 0.9 kg whereas patients receiving FO maintained their weight (0.5 ± 1.0 kg) ($P = .05$). Patients with the greatest increase in plasma EPA concentration after FO supplementation were found to have the greatest gains in muscle ($r^2 = 0.55$; $P = .01$). Approximately 69% of patients in the FO group gained or maintained muscle mass. Comparatively, only 29% of patients in the SOC group maintained muscle mass, and overall the SOC group lost 1 kg of muscle. No difference in total adipose tissue was observed between the 2 groups. **CONCLUSIONS:** Nutritional intervention with 2.2 g of FO per day appears to provide a benefit over SOC, resulting in the maintenance of weight and muscle mass during chemotherapy. ***Cancer* 2011;000:000–000.** © *2011 American Cancer Society.*

KEYWORDS: advanced cancer, computed tomography imaging, n-3 fatty acids, weight loss, cachexia, body composition.

Involuntary weight loss is common among patients with advanced cancer, contributing to poor treatment response, functional decline, and decreased survival.[1] Supplementation with >2 g per day of eicosapentaenoic acid (EPA) has been shown to stabilize weight loss,[2] attenuate lean tissue wasting,[3] and increase survival[4] in patients with advanced cancer. Conversely, 3 large phase 3 trials have failed to demonstrate a clear benefit of EPA with regard to body weight or lean tissue in cancer patients.[5-7] Possible reasons for this discordance are the time of the initiation of intervention, contamination between treatment arms, and indirect assessments of muscle mass. Studies have focused on patients who are advanced in the disease trajectory with a short median survival (in the study by Bruera et al,[8] the median survival was 14 weeks) and who are not receiving therapy because of progressive disease.[5,6] The results of these trials are difficult to interpret because of advanced wasting at the time of presentation (ranging from 2% to 56% of body weight) and a large number of early

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deaths. Compliance was not reported in 1 study,[7] and other studies have reported contamination of both the placebo and treatment groups.[2,6] In addition, previous studies have used indirect measures of skeletal muscle such as prediction of total lean body mass from total body water,[9] skinfolds,[8] and bioelectrical impedance,[2,5,6] none of which distinguish skeletal muscle from other lean soft tissue.

In patients with advanced cancer, an accelerated gain in lean tissue, including the liver and spleen, has been observed 3 months before death.[10] Therefore, making a specific distinction between skeletal muscle and other lean tissue is important. Computed tomography (CT) can precisely quantify skeletal muscle,[11] but to the best of our knowledge has not been previously used to assess the effect of EPA supplementation on skeletal muscle in patients with advanced cancer. CT imaging also distinguishes between different adipose depots (visceral, subcutaneous, and intermuscular) and was recently used to describe changes in adipose tissue in patients with advanced cancer, including accelerated loss of adipose tissue near the time of death.[12] Recently, muscle fat content has been recognized as a negative predictor of muscle strength.[13] Increased intermusclar adipose tissue (IMAT) has also been found to be correlated with poor function[14] and an increased incidence of mobility limitations.[14]

Patients receiving active treatment may represent an opportunity for timely nutritional intervention because side effects from chemotherapy such as nausea, vomiting, dysphagia, and anorexia often are disabling, and may impact on body weight and composition. This study uniquely used early intervention in newly referred patients with the goal of preventing weight and muscle loss during chemotherapy. The objective of the current study was to examine the effect of nutritional intervention with fish oil (FO) on weight and body composition against standard of care (SOC) during the course of chemotherapy.

MATERIALS AND METHODS

This study was approved by the Alberta Health Services Research Ethics Board. Written informed consent was obtained from all patients. At the Cross Cancer Institute in Edmonton, Alberta, Canada, which is 1 of 2 major cancer centers for all of Alberta, all newly referred patients with lung cancer attend a medical oncology clinic for new patients. At the clinic, patients are given a brief summary that describes available nutritional studies and are asked to indicate studies of interest. Patient response informs investigators which patients to approach regarding participation in research studies. To minimize bias and the recruitment of patients who are more motivated about nutrition into the intervention group, both arms were described as nutritional studies and patients were offered information regarding nutrient intake and body composition after the completion of both studies. If patients indicated they were interested in the intervention arm but subsequently declined to participate, they were not approached for the SOC arm.

Eligibility Criteria

Patients with a histologically confirmed diagnosis of non-small cell lung cancer (NSCLC) and who were naive to chemotherapy were eligible for enrolment. We included patients who were receiving first-line chemotherapy to maximize the accrual of patients for whom better survival would be predicted. All patients consented to receive platinum-based doublet chemotherapy with either curative or palliative intent based on standard practice specifically agreed on as clinical practice guidelines by the Alberta Provincial Lung Tumor Group. The duration of study was at least 6 weeks (2 cycles of chemotherapy). Patients with a CT image $\pm$ 45 days from the initiation of chemotherapy (mean, 25 $\pm$ 3 days) and a second CT image $\pm$ 45 days after receiving chemotherapy (mean, 21 $\pm$ 5 days) were included in the analyses. Because this study was aimed at preventing body composition changes from the time of treatment initiation, prior weight loss was not a criterion but self-reported weight loss within the 6 months preceding enrolment in the study was recorded from the Patient-Generated Subjective Global Assessment[15] or from patient history. Height and weight recorded on the same day by hospital staff was used for verification when available.

Study Design

To avoid the challenges of previous studies (contamination between treatment arms and poor compliance), the current study was designed as an open-label study with a contemporaneous control group. Patients meeting eligibility criteria consented to either nutritional intervention with FO or SOC (no intervention). SOC was comprised of blood draws and anthropometric measurements taken at the same time points as the FO group. To ensure patients recruited for the study were representative of the local advanced lung cancer population, we included a reference group to detail typical baseline characteristics of patients receiving first-line chemotherapy to provide

information concerning the expected changes in body composition during chemotherapy. Our research group has prospectively followed >600 patients with solid tumors of the lung for whom longitudinal CT images were available from the time of referral. Patient records were reviewed for the same inclusion criteria as patients in the SOC and FO groups: NSCLC diagnosis and naive to chemotherapy and treatment with first-line, platinum-based doublet chemotherapy. A total of 104 patients met the inclusion criteria. Subsequently, weight information was recorded and CT images were analyzed. CT images were obtained 95 ± 3.8 days apart. A mean of 19.5 ± 1 days elapsed between the initiation of chemotherapy and the first CT scan, and 18 ± 1.1 days elapsed between the second CT scan and the last day of chemotherapy.

Because previous studies have reported a benefit with ≥2 g of EPA,[3,16,17] patients were instructed to achieve a minimum intake of 2 g of EPA per day commencing on the first day of chemotherapy and continuing for the duration of their chemotherapy. Patients were given the choice of 2 formats of supplementation: 1) 4 + 1 g gelatin capsules per day containing 2.2 g of EPA or 2) 7.5 mL of liquid FO per day (2.2 g of EPA). Because poor compliance has been reported in previous studies,[2,5,6] we chose this approach to increase study adherence. Capsules were provided in kind by Ocean Nutrition Canada (Ocean Nutrition Canada, Nova Scotia, Canada). Liquid FO was purchased from NutraSea (Ascenta Health, Nova Scotia, Canada). These companies did not have access to the study results or influence the conclusions of the current study.

Blood was drawn by a registered nurse at the cancer center laboratory before the initiation of chemotherapy (baseline), 1 day before each 3-week cycle of chemotherapy, and on the last day of chemotherapy. Performance status was assessed by a physician using the Eastern Cooperative Oncology Group (ECOG) scale at baseline. Stage of disease was based on the American Joint Committee on Cancer stage groupings (I, II, III, and IV).[18] Response to treatment was evaluated by a radiologist and oncologist on the basis of clinical examination and imaging, which was comprised of CT, magnetic imaging resonance imaging, or x-ray.

Weight and Body Composition

Height was measured by a stadiometer and weight was measured using a medical balance beam scale at baseline and at each time point. Height and weight were used to compute body mass index (BMI) in kg/m^2. World Health Organization[19] categories were used to classify patients as underweight (BMI <18.5), normal (BMI 18.5 to 24.9), overweight (BMI of 25 to 29.9) and obese (BMI ≥30).

Body composition was analyzed using electronically stored CT images that had been obtained for diagnostic purposes. Cross-sectional areas (in cm^2) of skeletal muscle, IMAT, subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT) were determined using 2 consecutive images from the third lumbar vertebrae (L3) using sliceOmatic software (version 4.3; Tomovision, Montreal, Quebec, Canada). L3 was chosen as a landmark because it is reported to be strongly correlated with whole-body muscle and adipose tissue.[20,21] Mean tissue areas for 2 consecutive images were calculated and normalized for stature (cm^2/m^2). Total adipose tissue (TAT) was calculated by summing the IMAT, VAT, and SAT. Skeletal muscle attenuation, an indicator of muscle fat content,[22] was recorded. A lower value indicates increased fat infiltration and is associated with lower muscle strength and lower strength per muscle size (poor muscle quality).[13] The precision error for muscle attenuation using CT is <1%,[22] which makes it ideal for detecting longitudinal changes. Sex-specific cut-points for the L3 muscle index previously defined in an advanced cancer population[20] were used to designate patients as sarcopenic or nonsarcopenic. Males with <55.4 cm^2/m^2 of muscle and females with <38.9 cm^2/m^2 of muscle were classified as sarcopenic.

Changes in muscle and adipose tissue were expressed as the percentage change from the initial CT scan and divided by the number of days elapsed between the 2 CT images. The daily rate of change was multiplied by 100 to form a standard unit expressed as percentage change/100 days to allow for comparison between individuals. Because the precision error for muscle and adipose tissue is approximately 2%,[20] a change between −2 and +2 was considered maintenance of tissue. Total fat mass and total skeletal mass were estimated from cross-sectional areas as described by Shen et al[21]: skeletal muscle mass = 0.166 × [skeletal muscle greater than 5 cm higher than L4 to L5 (cm^2)] + 2.142 (r^2 = 0.855); fat mass = 0.068 × [total adipose at L3 (cm^2)] + 4.142 (r^2 = 0.927). A density of 1.04 g/cm^3 was used to convert muscle volume to mass.[23]

Compliance

The amount of supplement taken per day was recorded by the subjects and any unused capsules or liquid were returned at the time of patient visits. A compliance rate <80% resulted in withdrawal from the study.

Plasma Phospholipid Fatty Acid Analysis

Blood was collected in heparnized tubes and centrifuged to isolate plasma. Plasma was frozen immediately at −80°C until analysis. A chloroform-methanol solution (2:1, volume/volume) was used to extract plasma fatty acids and phospholipid (PL) was isolated on G-plates.[24] The PL band was scraped and C17:0 standard (1 mg/L) was added followed by direct methylation. Plasma PL fatty acid composition was determined by automated gas liquid chromatography (Varian 3600CX Gas Chromatograph; Varian, Missisauga, Canada) as previously described.[24] Peaks of saturated, monounsaturated, and polyunsaturated fatty acids between 6 and 24 carbon chain lengths were identified by comparison with a known standard (Supelco, Bellefonte, Penn, division of Sigma Chemical Company, St. Louis, Mo). Fatty acids were expressed as a quantitative amount (μg/mL) and as a percentage of the total PL.[25]

Statistical Analysis

The primary endpoint was change in muscle between baseline and the end of chemotherapy. Adipose tissue, body weight, and plasma EPA at baseline and at the end of chemotherapy were secondary endpoints.

Data are presented as the mean ± standard error (SE) and significance was determined at $P < .05$. All tests were 2 sided. The two-sample Student t test and chi-square test were used to determine differences between the SOC and FO groups. The reference data were collected during a different time period (2001 to 2007) then data from the SOC and FO groups. As such, data for the reference group are provided as a frame of reference and were not compared statistically with the SOC and FO groups. Repeated-measures analysis of variance with Bonferonni comparisons was used to analyze changes in tissue mass from baseline to the end of chemotherapy in the SOC and FO groups. Simple linear regression was used to examine the relation between muscle rate of change and plasma PL EPA. Statistical analyses were performed using SPSS statistical software (SPSS for Windows, version 17.0; SPSS Inc, Chicago, Ill).

RESULTS

Patient Characteristics

Patients were recruited over a 2-year period (2007-2009). A total of 204 patients were initially screened for inclusion criteria. Major reasons for exclusion included ineligible for chemotherapy, participation in a clinical trial (non-standard treatment), and <2 CT images available. Twenty-four patients were recruited to the SOC group and 17 patients were recruited to the FO group. All patients completed study protocol. One patient from the FO group was unable to achieve 80% compliance to the FO supplement and was subsequently excluded from analyses. There was no difference in treatment intent (19% received adjuvant therapy in the FO group vs 17% in the SOC group). The average time on study was comparable between the 2 groups (10.6 ± 0.8 weeks in the FO group and 9.8 ± 0.7 weeks in the SOC group; $P = .43$).

There were no significant differences with regard to baseline characteristics and anthropometric measures noted between the FO and SOC groups (Table 1). Patients recruited to the current study were representative of the local population because baseline characteristics were within the same range as the reference group. Although weight loss was not an inclusion criterion, a history of weight loss within the preceding 6 months was common. Despite this, >50% of patients were overweight or obese, similar to the reference population (53%).

Anthropometric Measurements

Patients in the SOC group lost significantly more weight than patients in the FO group (Table 2). In the SOC group, 29% of patients maintained or gained weight (0-4.6 kg) whereas 69% of patients receiving FO maintained or gained weight (0-6.7 kg) during chemotherapy. The amount of weight lost by the SOC group was similar to that of the reference group (Table 2).

Approximately 69% of patients in the FO group maintained or gained muscle compared with 29% of patients in the SOC group. Four patients in the SOC group became sarcopenic over the course of chemotherapy whereas no patients in the FO group became sarcopenic. One patient in the SOC group and 1 in the reference group had SAT outside the viewing field and were not included in TAT analyses. Changes in muscle, IMAT, and TAT over time are shown in Table 2. Tissue rate of change in the reference group fell within the same range as the rates observed in the SOC group.

Estimated whole-body skeletal and fat mass are shown in Table 3. Loss of skeletal mass was evident in patients in the SOC group, with some patients losing up to 5.2 kg of muscle from baseline to the end of treatment. Loss of skeletal muscle occurred concurrently with increased muscle fat content in the SOC group. Skeletal muscle attenuation decreased by approximately 3.5 HU in the SOC group (Table 3). This decrease represents an

Table 1. Baseline Characteristics and Anthropometric Parameters of Patients Receiving Standard of Care or Fish Oil, and a Cohort of Newly Referred Lung Cancer Patients to the Cross Cancer Institute[a,b]

Characteristic	Standard of Care Group	Fish Oil Group	Reference Group
Total, no.	24	16	104
Women, no. (%)	12 (50)	7 (44)	50 (48)
Men, no. (%)	12 (50)	9 (56)	54 (52)
Age, y	64 ± 1.8	63 ± 2.1	62 ± 1.0
AJCC stage			
III, no. (%)	8 (33)	5 (31)	32 (31)
IV, no. (%)	16 (67)	11 (69)	72 (69)
BMI, kg/m^2	27.3 ± 1.2	26.2 ± 1.1	25.9 ± 0.4
Weight loss in preceding 6 mo, %[c]	-4.2 ± 1.2	-6.3 ± 1.6	–
L3 SM area, cm^2	134.2 ± 6.1	134.9 ± 8.0	131.6 ± 3.1
Estimated whole-body SM, kg[d]	24.4 ± 1.0	25.4 ± 1.4	24.0 ± 0.5
Sarcopenic patients, %[e]	46	46	46
L3 total AT area, cm^2	349.7 ± 42.7	280.5 ± 42.2	272.1 ± 14.6
Estimated whole-body AT, kg[d]	27.9 ± 2.9	23.2 ± 2.9	22.6 ± 1.0
ECOG PS	1	1	–
ECOG range	0-2	0-2	–

AJCC indicates American Joint Committee on Cancer; BMI, body mass index; L3, third lumbar vertebrae; SM, skeletal muscle; AT, adipose tissue; ECOG PS, Eastern Cooperative Oncology Group performance status; –, data not available.
[a] The number of patients varies because of missing data as outlined in the Results section.
[b] Shown as the mean ± standard error. No significant differences were noted between groups ($P < .05$, two-sample Student *t* test and chi-square test).
[c] Data were not available from 3 patients.
[d] Derived from regression equations.[21]
[e] Based on cutpoints for muscularity.[20]

Table 2. Weight and Tissue Changes Quantified With CT Imaging From Baseline to After Chemotherapy in the Standard of Care, Fish Oil, and Reference Groups[a]

Changes	Standard of Care Group	Fish Oil Group	Reference Group
Weight change, kg	-2.3 ± 0.9	0.5 ± 1.0[b]	1.9 ± 0.3
Muscle rate of change, %/100 d	-6.8 ± 2.6	0.1 ± 1.6[b]	-6.0 ± 0.9
IMAT rate of change, %/100 d	9.5 ± 5.2	-16.4 ± 13.9[b]	11.1 ± 3.5
TAT rate of change, %/100 d	-3.9 ± 5.0	-5.0 ± 6.5	-6.0 ± 4.6

CT indicates computed tomography; IMAT, intermuscular adipose tissue; TAT, total adipose tissue.
[a] The number of patients varies because of images outside the viewing field. Results are shown as the mean ± standard error.
[b] Significantly different from standard of care ($P < .05$, using the two-sample Student *t* test.

approximate 3% increase in muscle fat content.[22] Similar loss of muscle mass (−0.9 kg ± 0.1 kg) and muscle attenuation (−2.8 HU ± 0.5 HU) was observed in the reference group.

Both tumor progression and FO supplementation may be related to loss of weight and muscle. To distinguish between the effect of tumor progression and FO, we compared treatment response between patients in the FO and SOC groups. No significant difference in treatment response was observed; 69% of patients (n = 11) in the FO group had stable disease or achieved a partial response to chemotherapy versus 67% of patients (n = 16) in the SOC group.

PL Analysis

Mean plasma PL EPA in the SOC group at baseline was comparable to EPA concentrations at the end of the study period. The mean plasma PL EPA in the FO group was increased more than 2-fold from baseline (Table 4). Despite a reported compliance rate of >95% (2.1 ± 0.6 g EPA/day), variability in plasma EPA was evident, with changes from baseline ranging from −0.3 to +3.8%. In view of this variation, regression analysis was used to examine the relation between EPA incorporation and muscle rate of change in the FO group (Fig. 1). There was a positive linear relation noted between change in plasma EPA concentration and rate of muscle change from baseline to the end of the study ($r^2 = 0.55$; $P = .01$).

Treatment Side Effects and Adverse Events

FO was well tolerated. No serious adverse events related to the study intervention were reported.

Table 3. Body Composition of Patients Receiving Standard of Care or Fish Oil Supplementation Using CT Imaging[a]

Body Composition	Standard of Care Group			Fish Oil Group		
	Baseline	End of Treatment	*P*	Baseline	End of Treatment	*P*
Whole-body SM, kg[b]	24.4 ± 1.0	23.5 ± 1.0	.002	25.4 ± 1.4	25.4 ± 1.5	.97
Whole-body AT, kg[b]	27.9 ± 2.9	27.6 ± 3.1	.74	23.2 ± 2.9	22.9 ± 1.4	.68
Muscle attenuation, HU	33.6 ± 1.7	30.1 ± 1.7	<.0001	33.2 ± 2.1	34.2 ± 1.9	.45

CT indicates computed tomography; SM, skeletal muscle; AT, adipose tissue; HU, Hounsfield units.
[a] The number of patients varies because of images outside the viewing field. Results are shown as the mean ± standard error (repeated-measures analysis of variance with Bonferroni pairwise comparisons).
[b] Estimated from regression equations.[21]

Table 4. Plasma PL EPA in the Standard of Care and Fish Oil Groups at Baseline and at the End of the Study Period[a]

	Standard of Care Group (n = 24)			Fish Oil Group (n = 16)		
	Baseline	End of Treatment	*P*	Baseline	End of Treatment	*P*
Amount of EPA, μg/mL	7.1 ± 0.8	6.5 ± 0.6	.53	8.0 ± 0.9	26.4 ± 2.2	<.0001
Proportion of EPA, %	1.0 ± 0.1	1.0 ± 0.1	.86	1.2 ± 0.1	3.7 ± 0.3	<.0001

PL indicates phospholipid; EPA, eicosapentaenoic acid.
[a] Results are shown as the mean ± standard error (two-sample Student *t* test).

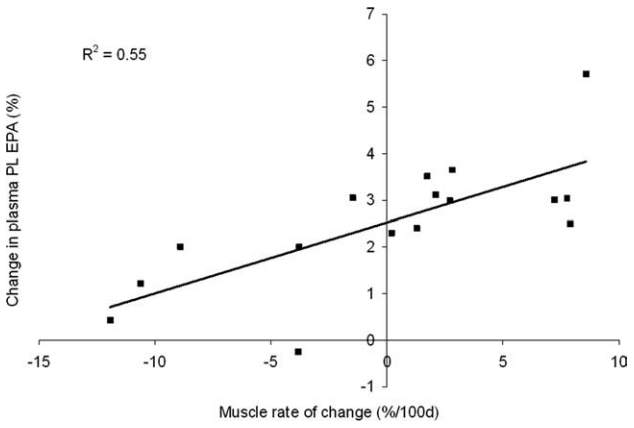

Figure 1. Relation between change in plasma phospholipid (PL) eicosapentaenoic acid (EPA) and change in muscle from baseline to end of fish oil supplementation is shown (n = 16).

DISCUSSION

The efficacy of FO to prevent muscle loss has been the focus of several studies,[2-9] but to the best of our knowledge the current study is the first to use CT images to provide a direct measurement of the effect of FO on skeletal muscle and adipose tissue depots. The results indicate that supplementation with FO ameliorates muscle and adipose tissue wasting in lung cancer patients and provides a benefit over patients treated with SOC receiving first-line chemotherapy.

On average, patients receiving FO maintained muscle mass, but the rate of muscle change varied. In addition, the concentration of plasma PL EPA after FO supplementation was variable despite high compliance with the FO supplement regimen. It is unlikely the variation in plasma PL concentration was solely because of misreporting of intake as a prior study in cancer patients also observed differential incorporation of n-3 fatty acids into plasma PL.[26] Regression analysis demonstrated a positive relation between increasing concentration of EPA and rate of muscle gain, with 55% of the variability in muscle change explained by plasma EPA concentrations. We recently reported a relation between skeletal muscle and physiological concentrations of EPA.[27] However, with the exception of a trial conducted by Fearon et al,[5] previous studies have not related plasma EPA concentrations with body composition. Rather, plasma EPA was used as a measure of compliance[2,8,28] or was not reported.[7] Because EPA must be incorporated into cells and tissues to exert physiological functions, we conjecture that failure to account for differential EPA incorporation limits the interpretation of prior studies and explains why the efficacy of EPA to promote muscle gain has not been consistently demonstrated.

Patients receiving FO maintained weight, muscle mass, and adipose tissue throughout approximately 10 weeks of chemotherapy despite presenting with mean weight loss of 6.3% over the previous 6 months. This supports findings of earlier trials that demonstrated a benefit of FO with regard to weight and lean body mass.[2,3] Improvements in weight have been reported in chemotherapy trials[29] and we acknowledge that the maintenance of weight and muscle mass reported herein cannot be solely attributed to FO intervention. However, both the SOC and FO groups were found to have similar chemotherapy response rates. Maintenance of body composition may have additional clinical implications because weight and tissue loss have been shown to influence performance status[1] and may dictate a patient's eligibility for additional lines of treatment. Therefore, targeting those patients receiving first-line chemotherapy represents an opportunity for timely intervention to prevent the deterioration of body composition.

To our knowledge, the relation between IMAT and skeletal muscle in cancer patients has not been previously explored and the observation that FO supplementation results in loss of IMAT while maintaining muscle mass is novel. IMAT accumulation is correlated with insulin resistance,[30,31] which has been implicated in the development of cancer cachexia.[32] Increased fat infiltration of skeletal muscle has also been observed with weight gain.[22] Although greater than two-thirds of the FO group maintained or gained weight, this was not reflected in IMAT accumulation or muscle attenuation values. We hypothesize that EPA may function to decrease IMAT via its ability to suppress lipogenesis,[33] thereby reducing the deposition of lipids in muscle. In addition, EPA supplementation has been shown to reduce fat accumulation via stimulation of lipid oxidation.[34] The functional significance of this requires clarification and will be the focus of future work.

The current study focused on intervention in newly referred patients, to prevent deterioration of body composition and weight loss. Previous studies have treated patients who were close to death and had severe weight loss,[5,7,28] in whom intervention with a single agent may be limited. Selecting newly referred patients enabled the accrual of patients with better survival prospects, thus avoiding patient morbidity, which has complicated the results of prior trials.[6,7] In addition, offering patients 2 formats of FO supplementation resulted in high compliance to the supplements, with only 1 of 17 patients reporting a compliance rate $<80\%$. This represents a 25% increase in compliance compared with prior studies,[2,6,8] and may explain why our results demonstrated the efficacy of FO on muscle mass whereas the results of other trials were inconsistent.[2,6,7] Providing patients with a choice of supplement format may be a potential approach to strengthen compliance in future trials.

At our cancer center, patients receiving treatment with palliative intent (who comprised $>80\%$ of the patient population in the current study) have expressed low interest in participation in randomized studies. The unique use of a nonrandomized, open-label design resulted in timely study enrolment, improved compliance, and no reports of contamination between treatment arms. Although the current study was an open-label design, we believe the results are strengthened by the inclusion of a larger reference group of patients with NSCLC from our cancer center. The patients in the SOC and FO groups shared similar baseline characteristics as patients in the reference group and the changes in weight and body composition observed in the SOC group during chemotherapy were comparable to those noted in the reference group.

Early intervention with FO during chemotherapy resulted in maintenance of weight, muscle mass, and muscle quality compared with patients receiving SOC. However, the results of the current study require verification in larger randomized trials. Because the incorporation of EPA in PL varies greatly between individuals, future trials should stratify outcomes based on the incorporation of EPA. The use of FO as a therapy to prevent body composition changes in patient populations who are at an increased risk of developing cancer cachexia merits further investigation.

CONFLICT OF INTEREST DISCLOSURES

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