Therapeutic Nutrition for People With Cancer

PROSURE® PRODUCT MONOGRAPH

Learn more about ProSure®
and how it can help keep cachexia
from interrupting patients' lives

Abbott
A Promise for Life

ABSTRACT

People with cancer often experience weight loss and decreased quality of life. Unintended weight loss is sometimes the first sign of cancer a patient notices, and is just one aspect of a more complicated condition known as cancer cachexia. Cachexia may also include anorexia, early satiety, fatigue, muscle loss, decreased strength and physical function. These impairments can lead to reduced tolerance to anticancer therapy, loss of independence, depression, anxiety, and decreased survival.

Cancer cachexia is caused by factors that are released by certain tumors and by the host's inflammatory response to the presence of the tumor. These factors depress appetite and impair the body's metabolism of dietary fat, protein, and carbohydrate. Such changes actually begin before weight loss is evident and can worsen as cancer progresses; stages of cachexia have recently been recognized as pre-cachexia, cachexia syndrome, and refractory cachexia. Cancer cachexia can be managed in part by special nutrition.

ProSure®, a therapeutic nutritional product, is scientifically formulated to help manage cancer cachexia and weight loss. Prosure® contains a high amount of protein to help build lean body mass, and it is calorically dense. ProSure® is enriched with eicosapentaenoic acid (EPA), which helps decrease the harmful metabolic changes induced by tumor-related factors. ProSure's® unique combination of EPA with protein- and energy-rich ingredients helps counter the physiological abnormalities that underlie weight loss due to cancer cachexia. For people with cancer, ProSure® is recommended as two 240-mL servings per day along with regular food consumption. Adding ProSure® to the diet does not inhibit usual meal intake.

ProSure® has additional features that make it desirable therapy for people with cancer—low fat content, fermentable fiber, a full complement of vitamins and minerals, and a less-sweet taste. ProSure® contains medium-chain triglycerides and is lower in fat than many standard nutritional supplements, so it is relatively easy to digest, well tolerated, and does not lead to early satiety. The short-chain fructooligosaccharide (scFOS) fiber component of ProSure® helps maintain digestive-tract health, even when food intake is reduced. scFOS helps manage diarrhea associated with cancer treatments such as chemotherapy or radiation, and scFOS also helps relieve constipation associated with pain medications. ProSure's® 28 added vitamins and minerals compensate for lowered food consumption due to anorexia and early satiety in people with cancer.

ProSure® is specifically preferred by patients. Based on taste-testing by people with cancer, ProSure® is formulated to be less-sweet than other nutritional products, and it is available in five patient-preferred flavors—banana, orange, vanilla, chocolate and café latte.

ProSure® is clinically proven to benefit people with cancer. If weight loss due to cancer cachexia is not effectively treated, poor outcomes can result. Such outcomes include decreased response to cancer treatments, increased frequency of complications and infections, and shortened survival. In addition to survival, people with cancer are particularly concerned about restoring and maintaining quality of life. Clinical studies demonstrate that drinking ProSure® daily as part of an overall cancer-care plan can effectively bring about weight gain, help build lean body mass, enhance strength in patients who gained weight, increase physical activity and functioning, and increase quality of life.

TABLE OF CONTENTS

OVERVIEW: PROSURE® AS THERAPEUTIC NUTRITION

THE PROBLEM: WEIGHT LOSS AND CACHEXIA IN PEOPLE WITH CANCER

Many people with cancer experience weight loss at some point during the course of their disease. Weight loss can be an early sign of an undiagnosed tumor. For some people, this early and unintended weight loss is the condition that prompts an initial doctor visit. For others, weight loss occurs only as the cancer and its treatment advance. Weight loss is evident in 31% to 87% of people with cancer, depending on tumor type.[1] Such weight loss is associated with poor outcomes for cancer patients—reduced response to therapy, more complications and infections, lower quality of life, and reduced survival. Most cancer patients are particularly troubled by reduced strength and loss of functional abilities, conditions that markedly lower their quality of life.[2]

An imbalance between nutritional needs and requirements can lead to cancer-induced weight loss, which may progress and ultimately result in refractory cachexia and death.[3] People with solid tumors—as in lung and gastrointestinal cancer—are likely to develop this type of weight loss.[4] Unintended weight loss in cancer patients is different from other types of weight loss (e.g., starvation or depression-associated weight loss) because it cannot be reversed by intake of additional calories.[5-7] In patients with cancer-associated weight loss, metabolism of nutrients is altered. As a result, trials of conventional therapy for cancer-induced weight loss have demonstrated little weight gain, and few or no improvements in functional ability, quality of life, or survival.[8-10]

Cachexia and unintended weight loss are due largely to metabolic changes in the cancer patient's body.[11, 12] Cachexia is initiated when proinflammatory cytokines and other catabolic factors, such as proteolysis-inducing factor (PIF) and lipid-mobilizing factor (LMF), are released in tissues and in circulation. These cytokines and catabolic factors are produced by the tumor or by the host in response to the tumor.[12-14] Therapy for weight loss in cancer patients should therefore target these specific inflammatory triggers and their resultant metabolic abnormalities.

THE SOLUTION: PROSURE®

ProSure® is a therapeutic nutritional product designed specifically for people who have experienced cancer-induced weight loss or for those who are at risk for such weight loss. ProSure® is a high-protein, energy-dense, low-fat formulation that contains an efficacious amount of eicosapentaenoic acid (EPA), a fish oil-derived omega-3 fatty acid. EPA effectively attenuates certain metabolic changes underlying cancer cachexia with weight loss.

KEY FEATURES OF PROSURE®

Importance of eicosapentaenoic acid (EPA)
EPA effectively attenuates metabolic change and the proinflammatory response that is associated with cancer-induced weight loss.

- **Clinically demonstrated efficacy.** Clinical studies support the use of ProSure® as part of an overall cancer-care program for patients with cancer-associated malnutrition and unintended weight loss.
- **Enriched with eicosapentaenoic acid (EPA).** EPA (at 1.1 g per 240-mL serving) is an omega-3 fatty acid that effectively attenuates certain metabolic changes underlying cancer-induced weight loss.
- **Macronutrient profile ideal for cancer patients experiencing unintended weight loss.** Sixty-one percent (61%) of the energy in ProSure® comes from carbohydrate, 21% from protein, and 18% from fat.
  - **High amount of high-quality protein to help build lean body mass.** ProSure® contains 16 g protein per 240-mL serving. ProSure® proteins are derived from milk, a source of high biologic value protein that contains all the essential amino acids.
  - **Low fat to help prevent early satiety and facilitate tolerance.** ProSure's® formula contains just 6 g fat per 240-mL serving, lower in fat than standard nutritional products.
  - **Sufficient carbohydrate to enable protein sparing.** ProSure® provides 44 g carbohydrate per 240-mL serving.
- **Calorically dense to provide concentrated nutrition in a small volume.** In a 240-mL serving, ProSure® provides approximately 1269 kJ (300 kcal) or 1.27 kcal/mL. ProSure® is recommended at the level of two 240-mL servings per day in addition to the patient's normal daily food consumption.
- **Beneficial ratio of omega-6 (n-6) to omega-3 (n-3) fatty acids (0.3 to 1.0).** ProSure® contains a higher level of n-3 fatty acids compared to n-6 fatty acids, thus helping reduce synthesis of inflammatory mediators associated with cancer cachexia and unintended weight loss.

ProSure® contains a unique blend of prebiotic fiber to help promote digestive tract health with EPA from fish oil and antioxidants to support immune health. ProSure® contains 5 g of a fermentable fiber blend per 240-mL serving with 2.6 g of short-chain fructooligosaccharide (in liquid ProSure®) to help manage diarrhea associated with cancer treatments (e.g., chemotherapy or radiation) and to help relieve constipation associated with pain medications. ProSure® contains 28 vitamins and minerals to help prevent or offset deficiencies when people with cancer have low dietary intake. ProSure® is lower in sucrose than standard nutritional supplements (7 g per 240-mL serving), providing a less-sweet taste that is preferred by many people with cancer. ProSure® is available in five pleasant-tasting flavors—banana, orange, vanilla, chocolate, and cafe latte—based on selections by people with cancer in worldwide taste-testing trials.

THERAPY FOR CANCER-ASSOCIATED WEIGHT LOSS AND CACHEXIA

This monograph summarizes what is presently known about cancer-associated weight loss and cachexia—frequency of occurrence, adverse effects on patient outcomes, and the biological mechanisms underlying these conditions.

The monograph also provides detailed information about ProSure® as a therapeutic nutritional product for people with cancer, including the rationale for ProSure® formulation, results of ProSure® clinical testing, and recommendations for its use. In patients with cancer and unintended weight loss, ProSure® has been clinically shown to help:

- Promote weight gain[15-28]
- Build or maintain lean body mass[15,17-19, 22, 24, 26, 29, 30]
- Improve appetite and dietary intake[15, 18, 19, 22, 23, 30-32]
- Attenuate the proinflammatory response[16,23, 24, 28-30, 33, 34]

ProSure® is also associated with:

- Increased strength in those who gained weight[35]
- Improved physical activity[15, 32, 36]
- Improved quality of life[18, 19, 23, 24, 30, 31, 35-37]
- Reduced treatment interruptions/toxicities[27, 30, 37, 38]

HIGHLIGHTS OF THIS MONOGRAPH

- Weight loss in people with cancer is a debilitating and life-threatening condition.
- Because of underlying metabolic abnormalities, cancer-associated weight loss is different from weight loss due to simple starvation (caloric deficiency).
- People with cancer cachexia and unintended weight loss can benefit from ProSure®—a nutritional therapy that provides an efficacious level of eicosapentaenoic acid in combination with a rich supply of energy and increased amounts of high-quality protein.
- In clinical studies, ProSure® therapeutic nutrition significantly improves muscle mass, physical activity, weight, and quality of life. These features are recognized as important outcomes for people with cancer.

CANCER CACHEXIA

A group of international experts in cancer cachexia research developed a definition, diagnostic criteria, and classification system specific to cancer cachexia.[3] They defined cancer cachexia as:

- a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.

The significance of early intervention

Early treatment of cancer-induced metabolic derangement can help prevent or delay the onset and progression of weight loss and skeletal muscle wasting that occurs with cachexia.

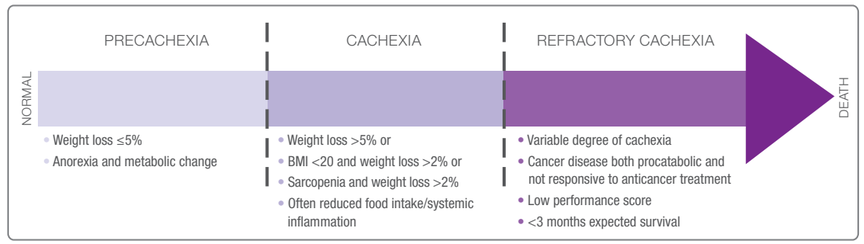
CANCER CACHEXIA IS DIAGNOSED BASED ON:

- Weight loss > 5% over the past six months (in absence of simple starvation); or
- BMI < 20 and any degree of weight loss > 2%; or
- Appendicular skeletal muscle index consistent with sarcopenia (males < 7.26 kg/m^2; females < 5.45 kg/m^2) and any degree of weight loss > 2%

STAGES OF CANCER CACHEXIA

Cancer cachexia can be classified into three stages that represent a continuum of clinical relevance: precachexia, cachexia, and refractory cachexia with the severity of depletion classified according to the ongoing rate of weight loss together with the degree of depletion of energy stores and body protein mass.[3] Clinical and metabolic signs are unique to each stage (Figure 1). Not all patients will move through all three stages. Risk of progression depends on tumor type and stage, presence of systemic inflammation, reduced food intake, and lack of response to anticancer treatment.

Figure 1
Stages of cancer cachexia



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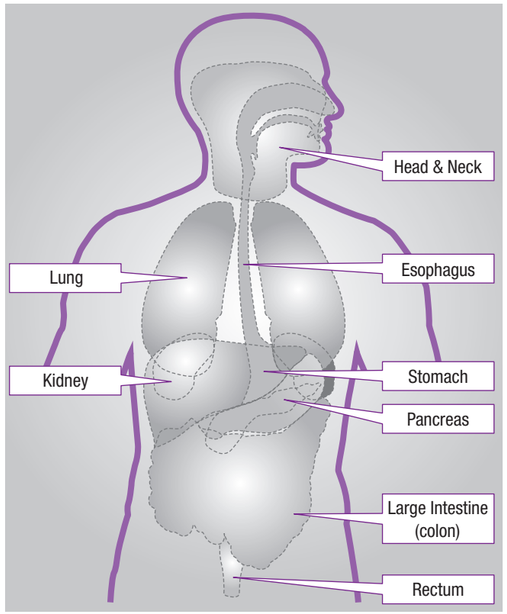
WEIGHT LOSS IN CANCER

PREVALENCE AND PROGRESSION

Up to 80% of people with cancer lose weight at some point in their disease depending on tumor type.[4] Moderate to severe weight loss occurs in 31% to 87% of patients, depending on tumor type.[1] Weight loss is more commonly associated with tumors of the lung and the gastrointestinal tract than with hematological malignancies or other solid tumors (Figure 2).[39]

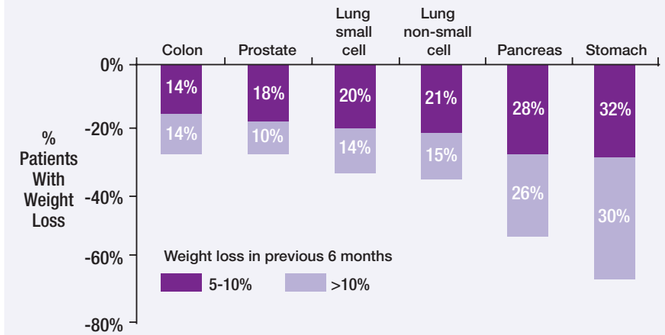
Figure 2
Cancer-induced weight loss occurs commonly in people with tumors of the lung or gastrointestinal tract.



DeWys et al examined the frequency and severity of weight loss in 3047 people with different tumor types; more than half of these patients lost weight, with 15% losing more than 10% of their usual weight (Figure 3).[1] The majority of terminally ill people with cancer experience severe weight loss; this weight loss accounts for at least 30% of cancer deaths in general, and up to 80% of deaths in patients with advanced pancreatic cancer.[6] Results of a study by Andreyev and colleagues showed that up to 70% of patients with gastrointestinal malignancies experienced weight loss.[40]

It is important to note that nutritional needs of people with cancer vary considerably, depending on the status of their disease and its treatment. Some may experience declining nutritional status before diagnosis—largely due to adverse impact of cancer on body metabolism. Others may experience negative impact of treatment (radiation, chemotherapy, or surgery) on their appetite and nutritional status. Still others may experience adverse nutritional consequences of both the cancer and its treatment.

Figure 3
Frequency and severity of weight loss in cancer patients[1]

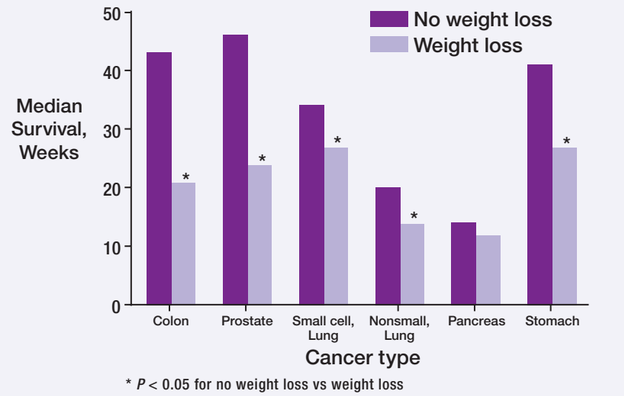


The weight-losing process begins early. Up to 80% of patients with advanced cancer (i.e., gastrointestinal, pancreatic, thoracic and head and neck) experience cachexia.[4] Metabolic alterations that result in cachexia are known to operate even before cancer is diagnosed or weight loss becomes apparent.[41] Mediators of inflammation and markers of hypermetabolism and catabolism are commonly detected in people with malignant tumors.[13, 41-43] Because processes underlying cancer-induced weight loss begin early in the disease course, early treatment can help prevent or delay the onset and progression of this debilitating and life-threatening sequence. Once cachexia is established, it may be difficult to improve the condition in all patients; however, the goal must be to stabilize cachexia to prevent or delay further decline.[7]

POOR OUTCOMES ASSOCIATED WITH WEIGHT LOSS

Response to therapy, quality of life, and survival are all negatively affected by weight loss associated with cancer. Weight loss is reported to be an independent predictor of poor survival (Figure 4).[1, 31, 40, 44] In fact, weight loss of just 5% can decrease both response to therapy and survival rate.[1, 40] Up to 20% of all cancer-related deaths are due to cachexia.[2, 39, 45]

Figure 4
Effect of weight loss on survival (adapted from DeWys et al)[1]



Cancer-induced weight loss adversely affects other outcomes (Table 1). Studies report increased length of hospitalization and more hospital readmissions among people with weight loss.[46] In addition, people with cancer who have lost weight have an increased susceptibility to infections and greater risks for treatment-related complications and toxicities.[40] Weight loss results in a negative body image, leading to anxiety, depression and reduced quality of life.[31, 47, 48]

Table 1
Poor outcomes associated with involuntary weight loss

- ↑ Morbidity and mortality
- ↑ Response to therapy
- ↑ Hospital length of stay and rate of readmissions
- ↑ Complications and infections
- Negative body image
- Depression
- ↑ Quality of life

CAUSES AND MECHANISMS OF WEIGHT LOSS

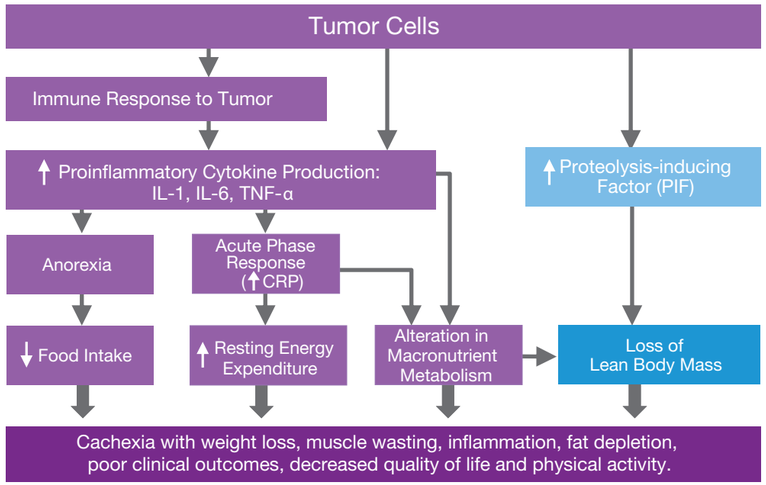
Cancer-induced weight loss is primarily caused by tumor-related factors that mediate adverse metabolic changes.[5] Weight loss may be worsened by other factors such as the tumor location, side effects of cancer treatment, or psychological issues.[49]

TUMOR-RELATED METABOLIC ABNORMALITIES

Researchers studying cancer-induced weight loss in the 1980s found that they could produce weight loss in a healthy rat by joining its circulation to that of a weight-losing rat with a solid tumor.[50] Based on these results, researchers concluded that tumor-related factors caused the loss of weight. In support of this conclusion, researchers found that the rat without the tumor regained weight if the rats were separated, and that both rats gained weight if they remained joined but the tumor was removed.

Since this first experiment, a number of substances has been experimentally shown to mediate cancer-induced weight loss. It is now recognized that specific alterations in metabolism are elicited along two separate but overlapping pathways (Figure 5). Proteolysis-inducing factor (PIF) and lipid-mobilizing factor (LMF) are released directly from tumors, while inflammatory cytokines such as tumor necrosis factor-α and interleukin-1 are part of the host's inflammatory response to the presence of a tumor.[12, 42, 51]

Figure 5
Etiology of cancer-induced weight loss



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Argiles JM, et al. *Curr Opin Clin Nutr Metab Care.* 2003;6(4):401-406.
Tisdale MJ. *Physiology (Bethesda).* 2005;20:340-348.
Tisdale MJ. *Physiol Rev.* 2009;89(2):381-410.

TUMOR FACTORS

Proteolysis-inducing factor (PIF)

In people with cancer, tumor expression of PIF has been correlated with weight loss, and PIF is present in their serum and urine.

Proteolysis-inducing factor (PIF). Proteolysis-inducing factor (PIF) was discovered several years ago as a unique circulating agent produced by tumors.[52] PIF is detected in the urine and serum of weight-losing people with a variety of different tumors.[16, 42] PIF is absent from the urine of cancer patients who are not experiencing weight loss, and PIF is likewise absent from the urine of weight-losing people who do not have cancer.[53]

PIF has been shown to induce loss of muscle by increasing protein degradation and by decreasing protein synthesis.[54] PIF directly induces the breakdown of proteins through activation of the ATP-ubiquitin-proteasome pathway.[55, 56] Along this pathway, proteins in body tissues are marked for degradation by covalent binding to ubiquitin molecules. Such marked proteins are selectively broken down in structures called proteasomes. In the presence of circulating PIF, lean body mass is rapidly depleted despite adequate dietary intake. PIF is not currently monitored in routine clinical practice, but is used more in research studies.

CYTOKINES AS MEDIATORS OF HOST RESPONSES

Acute-phase protein response (APPR)

Presence of the APPR in a patient with cancer distinguishes the condition of cancer-induced weight loss from other types of weight loss.

Proinflammatory cytokines. Tumor cells also initiate an inflammatory response, which results in the release of a number of substances (e.g., proinflammatory cytokines) into the bloodstream. These substances initiate the chain of events that leads to the major signs and symptoms of cancer-induced weight loss (Figure 5).

Changes in normal body metabolism that result from cytokine release include:

- Initiation of the acute phase protein response (APPR).
- Alterations in the metabolism of body stores of micronutrients.
- Suppression of appetite (anorexia).

Acute phase protein response. Cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), elicit a host response known as the acute phase protein response (APPR).[11, 57, 58] The APPR is the mechanism by which the body responds to stress, trauma, infection, inflammation, and cancer. The APPR increases the production of certain proteins, such as C-reactive protein (CRP),[11, 15, 57] which is a marker for the APPR.

Ideally, the APPR functions as a short-term defense mechanism to help the body heal and recover.[59, 60] The APPR can cause significant loss of lean body mass, increase resting metabolic rate (RMR; also called resting energy expenditure, REE), and can increase mortality.[59, 60] A C-reactive protein level >10 mg/L indicates an ongoing APPR that may contribute to weight loss.[60] The increased RMR in weight-losing patients with cancer leads to wasting of muscle and adipose tissue.[61] By contrast, in people with weight loss due to starvation (caloric deficiency), the RMR or REE actually decreases, thus conserving energy.

Altered macronutrient metabolism. Cytokines, hormones, and other tumor factors alter the metabolism of all three macronutrients—protein, carbohydrate, and fat—causing loss of both lean and non-lean body mass.[11, 12, 49] Specific metabolic alterations can enhance protein breakdown, increase lipolysis, and promote gluconeogenesis.

Altered glucose metabolism. In the relatively low-oxygen environment of a tumor, lactate is produced via the Cori cycle, and this lactate is in turn converted to glucose in the liver (gluconeogenesis).[12, 62] Production of glucose from lactate is highly inefficient and contributes to the increase in RMR seen in people with cancer.[12]

Insulin-stimulated glucose uptake by muscle is decreased because of peripheral insulin resistance.[63] This alteration redirects glucose to the liver and other viscera rather than to skeletal muscle.

Altered protein metabolism. Loss of body protein is due to a complex interaction of factors. Tumor-related factors, TNF-α and PIF, initiate skeletal muscle degradation through activation of the ATP-ubiquitin-proteasome pathway.[45] The unavailability of glucose to muscle cells also leads to oxidation of amino acids, thus exacerbating loss of lean body mass.[61]

Altered lipid metabolism. Loss of fat stores is also common in patients with cancer.[45, 64] Multiple factors—including TNF-α, lipid mobilizing factors (LMF), and alterations in activities of specific metabolic enzymes—cause a breakdown of adipose tissue. TNF-α inhibits lipoprotein lipase and triglyceride storage by adipocytes.[65] In addition, TNF-α activates hormone-sensitive lipase, which leads to breakdown of stored lipids in adipocytes. With inhibited lipid storage and activated lipolysis, loss of fat tissue occurs. LMF also acts directly on fat tissue to mobilize triglycerides. LMF is present in urine or serum of cancer patients experiencing weight loss, but not in patients losing weight due to other diseases.[66, 67]

Anorexia. In cancer-induced weight loss, released cytokines (TNF-α, and IL-1) produce appetite suppression by acting on hypothalamic food-intake regulatory areas of the brain.[68, 69] These cytokines may also inhibit food intake by prompting adipose tissues to release leptin, a satiety signal. IL-1 has also been shown to reduce appetite by suppressing neuropeptide Y (an appetite stimulant) in the hypothalamus.[70]

PHYSICAL, PHARMACOLOGICAL, AND PSYCHOLOGICAL FACTORS

While cancer-induced weight loss is largely mediated by substances produced directly or indirectly by tumors, other conditions exacerbate this weight loss by reducing food intake. These include tumor-related physical obstructions to food intake, nutrient absorption by the tumor, side-effects of cancer treatments, and psychological issues (stress and anxiety) that lead to anorexia or depression.

New observations indicate that factors such as the patient's age, level of physical activity, and the specifics of protein metabolism in hypermetabolic cancer patients should also be considered. These issues help explain why conventional nutrition support alone is usually an insufficient therapy for cancer cachexia.[71] In addition, reports suggest that genetic predisposition may also play a role in development of systemic inflammation and cancer cachexia; clinical exploration of this concept may lead to identification of specific biomarkers for cachexia.[72]

CANCER CACHEXIA VERSUS SIMPLE STARVATION AS A CAUSE OF WEIGHT LOSS

Simple starvation versus cachexia

In simple starvation, fat is used for energy and lean body mass is preserved. Cancer-induced weight loss is primarily due to loss of lean body mass.

Differentiating between cancer-induced weight loss and weight loss due to simple starvation (i.e., deficient caloric intake as in depression, malabsorption, and mechanical obstruction) is useful to help explain why nutrition support often fails to improve the nutritional status of people with cancer. In both instances, body weight, body fat, and lean body mass decrease (Table 2). However, in caloric deficiency, adaptive mechanisms preserve lean body mass by conserving energy expenditure and by reducing protein synthesis and degradation.[73] In weight loss due to caloric deficiency, metabolism shifts from glucose to fatty acids and ketone bodies as a fuel source, thus protecting lean body mass and prolonging survival. Weight loss due to caloric deficiency can usually be reversed when caloric intake is increased.[73]

In contrast to caloric deficiency, weight loss of cancer cachexia is characterized by metabolic abnormalities that decrease lean body mass. Nutrients are used inefficiently, extra energy is needed, and wasting of vital lean body mass occurs. Many people with cancer also develop insulin resistance and hyperglycemia, conditions that interfere with the ability of cells to obtain energy efficiently.[73]

Table 2
Nutritional alterations in cancer-induced weight loss and caloric deficiency

VARIABLE	CANCER CACHEXIA WITH WEIGHT LOSS	SIMPLE STARVATION WITH WEIGHT LOSS
Body weight	↓	↓
Lean body mass	↓↓	↓
Body fat	↓	↓↓
Total energy expenditure	↓	↓↓
Resting energy expenditure	↑↑	↓↓
Protein synthesis	↑/↓	↓↓
Protein degradation	↑↑	↓↓
Serum insulin	↑/↓	↓↓
Serum cortisol	↑↑	—

Adapted from Kotler.[73]
↑ increase; ↓ decrease; — no change; ↑↑ large increase; ↓↓ large decrease

WEIGHT-LOSS THERAPY: WHAT OUTCOMES SHOULD BE MEASURED?

When comparing nutritional strategies for treating people with cancer-induced weight loss, it is important to understand the strengths and limits of outcome measures that are used to establish efficacy.

For people with cancer, the overall goals of nutritional therapy are to prevent or reverse the weight loss that accompanies the disease, to maintain physical function, and to stabilize or improve quality of life. When people with cancer-induced weight loss are given nutritional therapy, both subjective and objective criteria can be employed to measure the effects. Traditional measures of outcome include weight gain, body composition, appetite, and dietary intake (Table 3). More recently, there is a growing emphasis on evaluating patient-centered outcomes such as quality of life, strength, physical activity, and overall functional status.[74, 75] When comparing nutritional strategies for treating people with cancer-induced weight loss, it is important to understand the strengths and limits of outcome measures that are used to establish efficacy.

Table 3
Nutrition therapy: outcome measures

Traditional measures of outcome

- Weight gain
- Body composition (lean body mass)
- Appetite
- Dietary intake
- Treatment interruptions

Patient-centered outcomes

- Quality of life (EORTC QLQ-30*; EuroQol EQ-5D†)
- Handgrip strength
- Physical activity level
- Performance status (e.g., Karnofsky Performance Scale, ECOG Performance Status‡)

* EORTC, European Organisation for Research and Treatment of Cancer
† EuroQol-5D, European quality of life five-dimensional survey
‡ ECOG, Eastern Cooperative Oncology Group

TRADITIONAL MEASURES OF OUTCOME

Weight

Weight loss is an important prognostic indicator in patients with cancer, and weight measurement was the focus of early studies of cancer survival. For example, 5% weight loss (i.e., 4 kg loss by an 80 kg man) was associated with decreased response to therapy and reduced survival rate.[1, 40] Conversely, weight gain was thought to represent a reversal of this harmful process. However, to ensure that added weight is not a result of fluid retention or increased adiposity, weight gain must be supported by evidence of increased lean body mass.

Appetite and dietary intake

Appetite and dietary intake have also been studied as indicators of nutritional status. Appetite can be assessed by a number of different methods, such as a visual analogue scale, which rates appetite sensation on a scale of 0 = lack of appetite to 100 = hunger or the FAACT (Functional Assessment of Anorexia/Cachexia Therapy) an 18-item measure of patients' perceptions of appetite in which participants score items from 0 (worst response) to 4 (best response).[76] These assessment tools can show appetite changes over time but do not reveal actual nutritional status. Similarly, dietary intake can be estimated with the use of a tool such as a three-day diet record to assess caloric intake and to estimate protein and vitamin/mineral consumption. While diaries can identify caloric deficiency as a contributor to weight loss in people with cancer, many such individuals lose weight despite seemingly adequate food consumption.

Body composition

To correctly delineate loss of muscle from loss of fat, both lean body mass and total weight must be determined. Body composition can be measured by anthropometry, bioelectrical impedance analysis, dual energy x-ray absorptiometry, magnetic resonance imaging, or computed tomography (CT) scans. As with total weight loss, loss of lean body mass is directly correlated with poor tolerance to treatment, decreased quality of life, and decreased survival.[48, 77-79]

Computed tomography (CT) image analysis and magnetic resonance imaging allow for the analysis of both skeletal muscle and adipose tissue. CT imaging can distinguish between different adipose deposits (visceral, subcutaneous, and intermuscular).[80] CT images are routinely available for most cancer patients for diagnosis and monitoring of treatment and disease progression and thus provide a way to monitor body composition over time. Image analysis software is available to analyze CT scans for body composition.

Skeletal muscle wasting can be identified with CT imaging. Loss of lean body mass may be obscured by body weight and can develop in both underweight and obese patients. Body mass index (BMI) does not reveal signs of muscle wasting.[81] Abdominal CT images of patients with the same BMI can show one with skeletal muscle wasting and one without. Cancer patients are now more likely to be overweight or obese and with muscle wasting rather than being clinically underweight. In a prospective cohort of 441 patients with non-small cell lung cancer, mean BMI was 24.9, with 47.4% of patients being overweight or obese, while only 7.5% were underweight (BMI < 18.5).[82]

Lean body mass: Effect on treatment tolerance and outcome

Baracos and Prado have published results of studies using CT images to evaluate cancer cachexia in patients with non-small cell lung cancer,[82] breast cancer,[83] solid tumors of the respiratory and gastrointestinal tracts[84] and renal cell carcinoma.[85] The presence of sarcopenia (loss of lean body mass) in cancer patients has been found to effect treatment tolerance. In a study of 55 women with metastatic breast cancer who were receiving capecitabine,[83] sarcopenia was found to be a factor in dose-limiting toxicity and treatment interruptions (dose reductions or delays). Twenty-five percent of the women in the study were classified as sarcopenic, which occurred in normal weight, overweight, and obese individuals. Toxicity developed in 50% of sarcopenic patients compared with only 20% of nonsarcopenic patients ($P = 0.03$). Patients with sarcopenia also experienced shorter time to tumor progression (101.4 days; confidence interval, 59.8-142.9) compared to nonsarcopenic patients (173.3 days; confidence interval, 126.1-220.5; $P = 0.05$). Because CT scans are available for most cancer patients, the authors feel that based on their study results, assessing body composition via CT scans has the potential to predict toxicity and individualize chemotherapy dosing.

A BMI < 25 kg/m^2 with sarcopenia was associated with dose-limiting toxicities in patients with renal cell carcinoma.[85] In patients with hepatocellular carcinoma treated with sorafenib, dose-limiting toxicity was observed in about 80% of sarcopenic patients with over 40% of the sarcopenic patients experiencing grade three/four diarrhea.[86] Mir et al[87] found similar results in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib. Patients with sarcopenia experienced significantly more dose-limiting toxicities than non-sarcopenic patients (82% versus 31%, $P = 0.005$). Grade three diarrhea was also significantly more frequent in sarcopenic patients than in non-sarcopenic patients (45.5% versus 6.9%, $P = 0.01$).

Sarcopenia has also been found to be associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. In patients with stage II-IV colorectal cancer (n=234), 38.9% were sarcopenic. Patients with sarcopenia experienced overall greater infection risk (23.7% vs 12.5%; $P = 0.025$) and longer length of stay (15.9±14.2 days vs 12.3±9.8 days, $P = 0.038$).[88]

Lean body mass: Effect on functional status and survival

Loss of lean body mass in patients with cancer has been shown to be associated with treatment toxicity, poor functional status and decreased survival

In a population based study of 2115 patients with solid tumors of the respiratory and gastrointestinal tracts, Prado et al[84] identified 325 (15%) as obese (BMI > 30). Using available CT scans for 250 of the obese patients, 38 (15%) were found to be sarcopenic. Patients with sarcopenic obesity had poorer functional status compared with obese patients who did not have sarcopenia ($P = 0.009$). Sarcopenic obesity was also found to be an independent predictor of survival (hazard ratio [HR] 4.2 [95% CI 2.4-7.2], $P < 0.0001$).

van Vledder and colleagues[89] retrospectively analyzed CT images of patients who had undergone resection of colorectal liver metastases to investigate the impact of sarcopenia and central obesity on survival. Of the 196 patients included in the study, 19.4% (38) were classified as having sarcopenia. Patients with sarcopenia had statistically lower five-year disease-free survival rates (15% versus 28.5% in patients without sarcopenia; $P = 0.002$) and overall survival rates (20% versus 49.9% respectively; $P < 0.001$).

PATIENT-CENTERED MEASURES OF OUTCOME

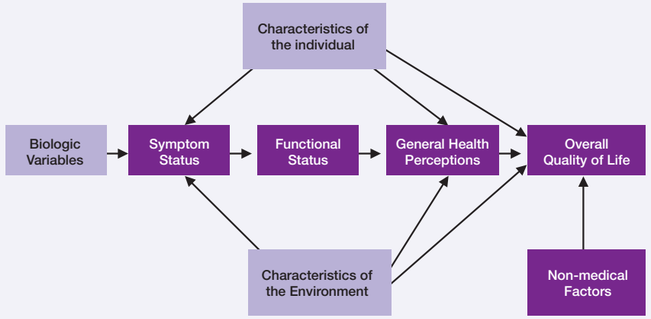
Quality of life. Quality of life (QOL) is very important to patients with cancer. In cancer treatment, there has been a gradual shift from use of objective response rates or survival as sole measures of treatment efficacy to consideration of quality of life and other patient-centered outcomes. Silvestri and colleagues asked 81 patients with non-small cell lung carcinoma who had experienced cisplatin-based chemotherapy, "What minimum survival benefit would justify acceptance of chemotherapy side-effects during treatment for advanced disease?"[90] Only 22% of the patients chose chemotherapy over supportive care alone for a realistic survival benefit of three months. By contrast, 68% chose chemotherapy if it would substantially reduce symptoms—even without prolonging life.

QOL research consists of two major areas: (1) health-related parameters and (2) broader determinants of well-being (sociological and economic determinants).

The concept of using QOL as a clinical indicator has been developed by Wilson and Cleary (Figure 6).[91]

QOL is very important to patients. In cancer treatment, there has been a gradual shift from use of objective response rates or survival as sole measures of treatment efficacy to consideration of quality of life and other patient-centered outcomes.

Figure 6
What factors contribute to quality of life?
Adapted from Wilson and Cleary, 1995[91]



This research team described five domains of QOL: biologic variables, symptoms, functional status, general health perceptions, and overall QOL. Biological variables are usually objective and determined by direct measures rather than by self-report (e.g., blood glucose level, blood pressure). Symptoms, functional status, and general health are usually reported by patients. Overall quality of life is also influenced by non-medical factors such as finances, employment, or family situations. Individual characteristics (mood, personality, preferences) and environmental characteristics (psychological and social support) also influence QOL. Different instruments for measuring QOL variously assess the contributing factors. These include EORTC QLQ-C30 and EuroQOL EQ-5S.

The EORTC QLQ-C30 is a multidimensional, cancer-specific quality of life questionnaire. Developed by the European Organisation for Research and Treatment of Cancer (EORTC) Study Group on quality of life, the questionnaire is designed for use with a wide range of populations of people with cancer.[92] Optional questionnaire modules can be used for specific cancer diagnostic groups or for specific cancer treatment modalities. The EORTC QLQ-C30 includes functional scales (physical, emotional, social, and cognitive functioning); symptom scales (fatigue, pain, and nausea and vomiting); a global health status and quality of life scale; and assessments for additional symptoms (dyspnea, sleep disturbance, constipation, and diarrhea), and perceived financial impact.

EuroQol EQ-5D is a generic, single-index measure of health status developed by a collaborative research network located in Europe.[93] EQ-5D questionnaires record the respondent's degree of difficulty with mobility, self-care, usual activity, pain and discomfort, and anxiety and depression. These data can be converted into a single-index score. The EQ-5D questionnaire also records the respondent's assessment of his or her overall health state on a visual analogue scale.

The ECOG (Eastern Cooperative Oncology Group) scale of performance status is widely used to quantify the functional status of cancer patients.[94] It is a four-point scale where PS-0 is normal activity; PS-1 is symptomatic but almost fully ambulatory; PS-2 means less than 50% of daytime in bed; PS-3 means more than 50% of daytime in bed; and PS-4 represents fully bedridden.

Strength. Handgrip strength is a measure of skeletal muscle function. An increase in handgrip strength reflects an improvement in muscle function. Assessing grip strength is simple, quick, noninvasive, and relatively inexpensive. A handgrip dynamometer is used.

Physical activity level. Physical activity level (PAL) is an objective measure of physical activity and an accurate surrogate for evaluation of functional status. Laboratory-based PAL measurements are labor-intensive and expensive, so PAL is used as a research tool rather than in routine clinical practice. PAL is calculated as the ratio between total energy expenditure (TEE) and resting energy expenditure (REE). TEE is measured by assessing metabolism of water with a "doubly-labeled water" technique**.** With this test, study subjects drink water labeled with two radioactive isotopes (deuterium and a stable isotope of oxygen), and their urine is collected for 24 hours. Isotope output provides a measure of how many calories the individual has used in a 24-hour study interval (i.e., combined calories used at rest and in activity) TEE. REE is quantified with indirect calorimetry (i.e., using a metabolic hood to measure the subject's oxygen consumption and carbon dioxide production over a fixed interval). A low TEE:REE ratio reflects a low PAL—an observation common to patients with cancer (Table 4).

Table 4
PAL score

SCORE	ACTIVITY LEVEL
1.0	Death
1.1	Near death
1.2 to 1.3	Very little activity or exercise (as in a person confined to bed)
1.5	Normal sedentary activity level (as in a person with an office job)
1.8	Active (as for a person who exercises vigorously)

PAL can also be estimated by use of a physical activity meter such as activPAL™ Professional.[95] The activPAL™ is about the size of a match box, is 7 mm thick, weighs about 20 g including the battery, and is designed to be worn for approximately seven days on the thigh. PAL provides accurate measurement of free-living physical activity, thus allowing clinicians and other professionals to assess patient compliance with exercise and treatment protocols and patient response to treatment interventions. The time spent standing and sitting/lying is recorded, and the number of transitions from sitting to standing, standing to sitting, and the number and cadence of steps is recorded.

Performance status. Performance status is a measurement that assesses an individual's ability to function independently. It is used to describe ability to work and carry out activities of daily living. The Karnofsky Performance Status is measured on a scale of 0 (dead) to 100 (normal), as shown in Table 5.[96] A score of 60 indicates that the individual requires occasional assistance with activities of daily living but is able to care for most needs.

Table 5
Karnofsky Performance Status

SCALE	PERFORMANCE
100	Normal. No complaints or no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of the disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal home activity or do active work
60	Requires occasional assistance but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death is not imminent
20	Very sick; hospitalization necessary; active supportive treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Deceased

NUTRITION SCREENING

Nutrition screening can help identify patients at risk of developing malnutrition or who are malnourished. A number of screening tools have been validated for use in oncology patients.

The Malnutrition Screening Tool (MST) has been validated for use in oncology outpatients receiving chemotherapy[97] and radiotherapy.[98] This tool contains two questions about weight history and appetite. It is a quick and simple tool.[99]

Patient-Generated Subjective Global Assessment (PG-SGA) is a two-part screening tool in which the patient completes the first part of the assessment. The patient answers questions regarding weight history, food intake, symptoms that affect eating, and general activity and function. The second part is completed by a healthcare professional and includes a physical assessment, assessment of metabolic stress, and disease-related nutrient demand.[99] A score is applied to the domains assessed by the patient and a three-level rating is determined: A-well nourished; B-moderately malnourished or suspected malnutrition; C-severely malnourished.

Identification of malnutrition from screening leads to a more in-depth nutritional assessment and the development of appropriate nutritional interventions with the goal of improving clinical outcomes.

EVIDENCE-BASED GUIDELINES

A number of evidence-based guidelines has been published that provide guidance on nutritional care in head and neck cancer patients, patients with cancer cachexia, patients receiving radiotherapy and chemotherapy, and patients requiring enteral or parenteral nutrition support (Table 6).

Table 6
Evidence-based guidelines

GUIDELINES	SOURCE
Nutritional management of adult patients with head and neck cancer	http://wiki.cancer.org.au/australia/COSA:Head_and_neck_cancer_nutrition_guidelines
Nutritional management of cancer cachexia	*Nutrition and Dietetics.* 2006;63(Suppl.2):S3-32. or www.daa.asn.au
Nutritional management of patients receiving radiation therapy	*Nutrition and Dietetics.* 2008;65(Suppl.1):S1-S20. or www.daa.asn.au
Enteral and parenteral nutrition support	EN: Surgery including Organ Transplantation. *Clin Nutr.* 2006;5:224-244. EN: Non-Surgical Oncology. *Clin Nutr.* 2006;25:245-259. Nutrition Support Therapy During Adult Anticancer Treatment and in Hematopoietic Cell Transplantation. *JPEN J Parenter Enteral Nutr.* 2009;33:472-500.

CONVENTIONAL NUTRITIONAL THERAPIES AND WEIGHT LOSS

Total parenteral nutrition (TPN), tube feeding, oral nutritional supplementation, nutrition counseling, and pharmacologic agents have all been used in attempts to improve nutritional status and quality of life for people with cancer.[9, 11, 100]

TOTAL PARENTERAL NUTRITION

In clinical studies, cancer patients who received TPN in conjunction with chemotherapy had a lower survival rate than did people receiving chemotherapy alone.[101] A meta-analysis of multiple studies concluded that only patients who were severely malnourished benefited from TPN supplementation.[102] The American College of Physicians discourages the use of TPN in cancer patients undergoing chemotherapy; these experts recommend further trials to identify patient subgroups that would benefit from nutrition support.[103]

ENTERAL NUTRITION

Enteral nutrition may be appropriate for people who are unable to eat but who have retained at least partial gastrointestinal (GI) function. Compared to parenteral feeding, tube feeding has the advantage of maintaining the gut-mucosal barrier.[104] A reduction in postoperative infections and decreased length of hospital stay have been reported in enterally fed oncology patients.[105, 106] However, few randomized controlled trials have been conducted in people with cancer receiving total enteral nutrition; larger, prospective studies are needed.

NUTRITIONAL COUNSELING AND ORAL SUPPLEMENTATION

Nutritional counseling, including the encouragement of oral supplements, is a strategy commonly used to improve oral intake and promote weight gain in people with cancer. Evans and co-workers studied 192 weight-losing individuals with advanced colorectal cancer or advanced non-small cell lung cancer.[8] Patients were randomized to an *ad libitum* diet group or to one of two nutrition-counseling groups that also received standard oral supplements. The nutrition-counseling groups increased their food intake; however, there was no difference in the 12-week weight-loss patterns between the counseled and control groups. In addition, no differences were detected in toxicity of chemotherapy, response to therapy, or survival across the three groups.

In another study, Ovesen et al examined 105 people with breast, ovarian, or small cell lung cancer. Patients were randomized to receive nutrition counseling with a choice of oral supplements or an *ad libitum* diet.[9] Patients undergoing chemotherapy were followed for five months. The nutrition-counseling group increased their mean energy intake over the study period. Despite the increase in energy intake in the nutrition-counseling group, increase in body weight was not significantly different between the treatment groups at the end of the five-month period. Furthermore, survival rate, response to therapy, and quality of life measures were similar between the two groups.

Isenring et al evaluated outcome benefits of using the American Dietetic Association medical nutrition therapy protocol (ADA MNT) compared with standard practice for patients undergoing radiation treatment for GI or head and neck cancers (n=29 intervention; n=31 standard practice; study interval = 12 weeks).[107] The protocol involved intensive intervention with nutritional counseling, specific diet advice, and addition of twice-daily servings of energy- and protein-rich oral nutritional supplements as needed. Study results demonstrated that nutrition intervention using the ADA MNT radiation oncology protocol led to improved dietary intake and quality of life, and less deterioration of nutritional status when compared to standard practice. Both patient groups experienced weight loss during the study interval, although patients on the ADA MNT protocol lost less weight.

Ravasco and colleagues conducted a randomized, controlled trial in patients with head and neck cancer to evaluate the effect of dietary counseling or oral supplements on nutritional outcome, morbidity, and quality of life (QOL) during and three months after radiotherapy.[108] Patients were randomized to one of three groups: group one (n = 25) dietary counseling with regular foods; group two (n = 25), usual diet plus supplements; and group three (n = 25), *ad libitum* intake.

In both the dietary counseling and supplement groups, energy intake increased after radiotherapy, ($P < .05$) as did protein intake, ($P < .006$). However, in group three, a significant decrease in both energy and protein intake was found ($P < .01$). More than 90% of the patients experienced toxicity, with a trend for reduced symptoms in the dietary counseling group. Quality of life function scores improved ($P < .003$) after radiotherapy in proportion to nutritional intake in groups one and two ($P < .05$), but worsened in group three ($P < .05$). Patients in group one maintained or improved overall QOL at three months, whereas patients in groups two and three maintained or worsened overall QOL.[108]

In a similar study design, Ravasco and colleagues evaluated the effect of dietary counseling or nutritional supplements on nutritional outcome, morbidity, and quality of life (QOL) during and three months after radiotherapy in 111 outpatients with colorectal cancer.[109] Patients were randomized to one of three groups: group one (n = 37), dietary counseling (regular foods); group two (n = 37), protein supplements; and group three (n = 37), *ad libitum* intake.

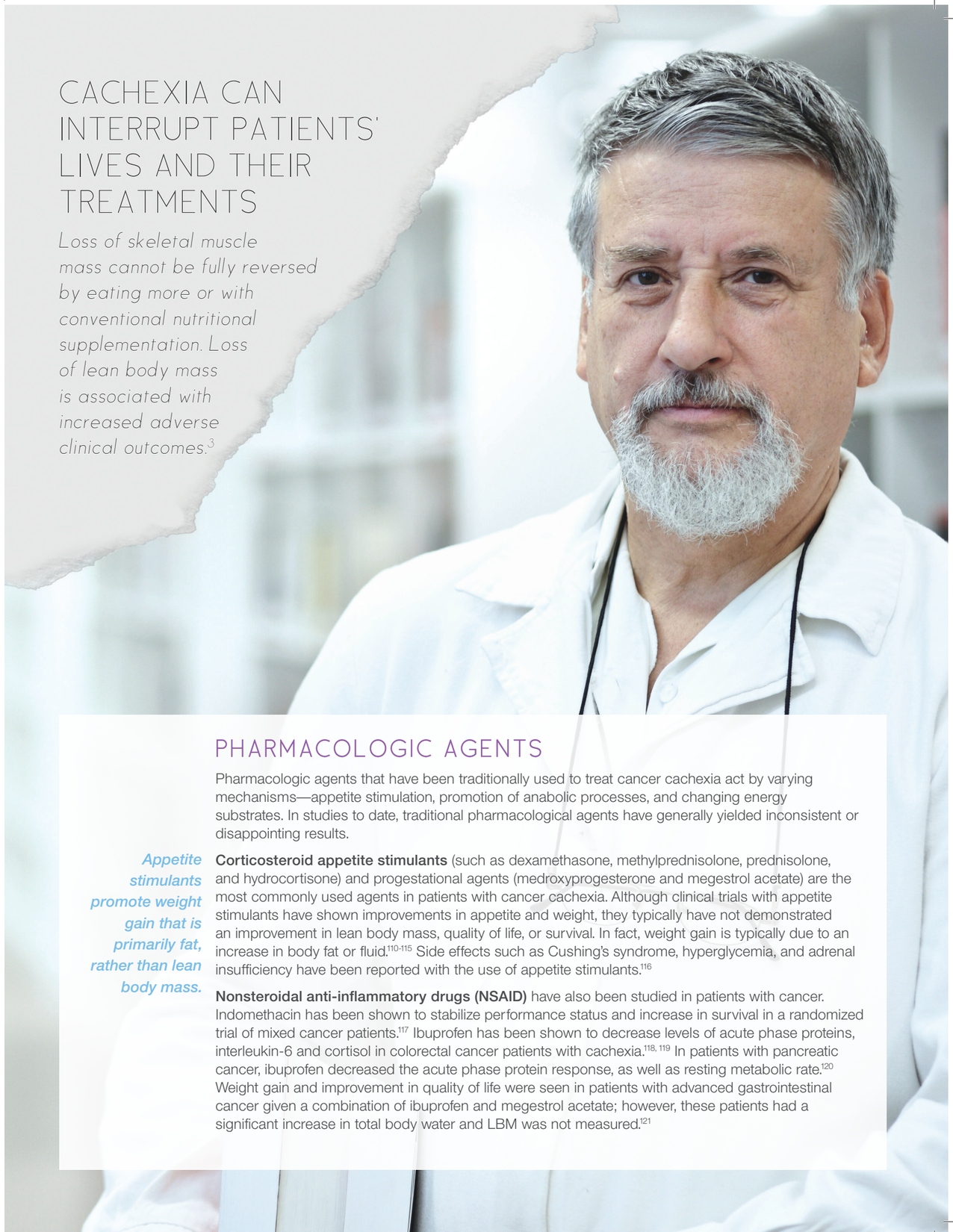
After completion of radiotherapy, patients in the groups who received dietary counseling and protein supplements were able to increase energy and protein intake ($P \leq .04$ and $P \leq .007$, respectively), whereas a decrease was found in group three ($P < .01$). Nutritional intake was maintained at three months in the dietary counseling group, whereas group two and three returned to baseline intake.

At radiotherapy completion, QOL function scores in the dietary counseling group improved proportionally to adequate intake or nutritional status ($P < .05$); whereas in group two only half of the function scores improved proportionally to protein intake ($P = .04$), and all scores worsened in group three ($P < .05$).[109]

A systematic review and meta-analysis of thirteen studies that included 1414 cancer patients evaluated the effect of oral nutritional interventions (defined as dietary advice, oral nutritional supplements, or both) in malnourished patients with cancer. Nutritional intervention was found to result in statistically significant improvements in weight and energy intake. Some aspects of quality of life (emotional functioning, dyspnea, loss of appetite, and global QOL) also showed improvement, but there was no effect on mortality.[10]

CACHEXIA CAN INTERRUPT PATIENTS' LIVES AND THEIR TREATMENTS

Loss of skeletal muscle mass cannot be fully reversed by eating more or with conventional nutritional supplementation. Loss of lean body mass is associated with increased adverse clinical outcomes.[3]



PHARMACOLOGIC AGENTS

Pharmacologic agents that have been traditionally used to treat cancer cachexia act by varying mechanisms—appetite stimulation, promotion of anabolic processes, and changing energy substrates. In studies to date, traditional pharmacological agents have generally yielded inconsistent or disappointing results.

Appetite stimulants promote weight gain that is primarily fat, rather than lean body mass.

Corticosteroid appetite stimulants (such as dexamethasone, methylprednisolone, prednisolone, and hydrocortisone) and progestational agents (medroxyprogesterone and megestrol acetate) are the most commonly used agents in patients with cancer cachexia. Although clinical trials with appetite stimulants have shown improvements in appetite and weight, they typically have not demonstrated an improvement in lean body mass, quality of life, or survival. In fact, weight gain is typically due to an increase in body fat or fluid.[110-115] Side effects such as Cushing's syndrome, hyperglycemia, and adrenal insufficiency have been reported with the use of appetite stimulants.[116]

Nonsteroidal anti-inflammatory drugs (NSAID) have also been studied in patients with cancer. Indomethacin has been shown to stabilize performance status and increase in survival in a randomized trial of mixed cancer patients.[117] Ibuprofen has been shown to decrease levels of acute phase proteins, interleukin-6 and cortisol in colorectal cancer patients with cachexia.[118, 119] In patients with pancreatic cancer, ibuprofen decreased the acute phase protein response, as well as resting metabolic rate.[120] Weight gain and improvement in quality of life were seen in patients with advanced gastrointestinal cancer given a combination of ibuprofen and megestrol acetate; however, these patients had a significant increase in total body water and LBM was not measured.[121]

INNOVATIVE THERAPY WITH EICOSAPENTAENOIC ACID

Clinical trials have demonstrated that increasing dietary intake is not usually effective for treating cancer-induced weight loss.[8, 9] Since cancer-induced weight loss is the result of inadequate energy intake, increased REE, and the complex interaction of many metabolic mediators, treatment can succeed only when underlying metabolic changes are addressed.[122] The inclusion of metabolically-active substrate eicosapentaenoic acid (EPA) in the diet is now recognized to be helpful in interfering with mechanisms underlying metabolic perturbations of cachexia.[123]

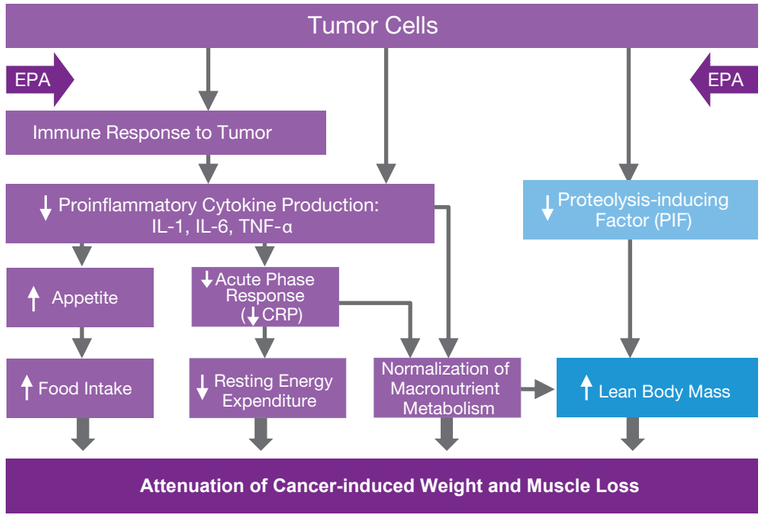
EPA is a long-chain polyunsaturated fatty acid (PUFA) of the omega-3 (n-3) family (Figure 7) and is found naturally in deep-sea oily fish (e.g., salmon, mackerel, herring, sardines, and tuna). EPA has been introduced as a nutritional supplement for people with cancer because it attenuates metabolic anomalies of cancer-induced weight loss and has been shown to stabilize weight.[16, 54, 124, 126, 128, 129]

Figure 7
Chemical structure of eicosapentaenoic acid (EPA)

EICOSAPENTAENOIC ACID: MECHANISM OF ACTION

EPA supplementation reduces production of proinflammatory cytokines such as IL-1, IL-6, and TNF-α and reduces the activity of PIF (Figure 8).[16, 54, 124, 126, 128, 129]

Figure 8
Role of EPA in the attenuation of cancer-induced weight loss



Wigmore SJ, et al. *Nutrition*. Jan 1996;12(1 Suppl):S27-30.
Wigmore SJ, et al. *Clin Sci* (Lond). Feb 1997;92(2):215-221.
Barber MD, et al. *Nutr Cancer*. 2001;40:118-124.
Endres S, et al. *N Engl J Med*. Feb 2 1989;320(5):265-271.
Jho D, et al. *Am Surg*. Jan 2003;69(1):32-36.
Lorite MJ, et al. *Br J Cancer*. 1997;76(8):1035-1040.

Skeletal muscle. Cachexia-inducing tumors produce and release the glycoprotein proteolysis-inducing factor (PIF) into circulation. PIF interacts with skeletal muscle and mediates loss of lean body mass by mechanisms that involve decreased protein synthesis and increased protein degradation.[54, 56, 124, 130] Binding of PIF to receptors on the surface of skeletal muscle cells results in release of arachidonic acid (AA) from membrane phospholipids. AA is metabolized to prostaglandin E_2 and other eicosanoids. One of the metabolites (15-hydroxyeicosatetraenoic acid) serves as an intracellular mediator that in turn increases degradation of myofibril proteins via the ubiquitin-proteasome proteolytic pathway. With dietary intake of EPA, cell membrane AA content is partially replaced by EPA, thus reducing the potential for release of the eicosanoid mediators of protein degradation. Pretreatment of animals with EPA completely abolished the cachectic effect of PIF and also prevented weight loss in mice bearing tumors.[131, 132]

Macrophages

As in the skeletal muscle cell, dietary sources of fatty acids influence the composition of the phospholipid bilayer in macrophage cell membranes. Dietary EPA replacement of AA has been shown to alter second messenger signaling systems within the macrophage, thus reducing production of inflammatory cytokines.[124]

Cell and Animal Studies

Cell and animal studies indicate that EPA inhibits tumor growth and works as a counter-regulator of tumor-produced mediators that lead to weight loss. EPA has attenuated the growth of a number of human carcinoma cell lines *in vitro*.[125, 130] Karmali and colleagues first observed EPA as an inhibitor of tumor growth in rats,[133] and subsequently found n-3 fatty acids to have a protective effect on the development and progression of a number of different tumor models.

Human Studies

Human studies involving fish oil and pure EPA capsules have shown that EPA stabilizes weight by moderating some of the underlying metabolic abnormalities. Slowed or reversed weight loss by EPA is thought to occur by:

- Decreasing the inflammatory response, as demonstrated by decreased production of pro-inflammatory cytokines[16]
- Decreasing the level and activity of PIF[16]

MURPHY STUDY, 2011[134]

Murphy et al evaluated the effect of fish oil supplementation (2.2 g/day) compared to standard of care on weight, skeletal muscle, and adipose tissue in 40 patients with non-small cell lung cancer receiving first-line chemotherapy. Body composition was assessed using CT scans. After approximately six weeks, patients in the standard of care group experienced an average weight loss of -2.3 ± 0.9 kg whereas patients in the fish oil group maintained their weight, 0.5 ± 1.0 kg; $P = .05$. Muscle was maintained or gained in approximately 69% of patients in the fish oil group compared with 29% of patients in the standard of care group. Over the course of chemotherapy, four patients in the standard of care group became sarcopenic compared to none of the patients in the fish oil group. In patients with non-small cell lung cancer receiving chemotherapy, a nutritional intervention with 2.2 g of fish oil per day appears to provide a benefit over standard of care in maintaining weight and muscle mass.

MURPHY STUDY, 2011[135]

Murphy et al evaluated the effect of the combination of fish oil and chemotherapy on response rate and clinical benefit over standard of care in patients with advanced non-small cell lung cancer. In this open-label trial, 46 patients completed the study (n = 31 in the standard of care group; n = 15 in the fish oil group [2.2 g EPA + 500 mg DHA/day]). Patients in the fish oil group were found to have an increased response rate (defined as the sum of complete response plus partial response) and greater clinical benefit (defined as the sum of complete response, partial response, and stable disease divided by the number of patients) compared with the standard of care group (60.0% versus 25.8%, $P = .008$; 80.0% versus 41.9%, $P = .02$, respectively). One-year survival was also found to be greater in the fish oil group (60.0% versus 38.7%, $P = .15$). The incidence of dose-limiting toxicities did not differ between the groups. These results suggest that fish oil supplementation can increase chemotherapy efficacy and may increase survival compared to standard of care in patients with advanced non-small cell lung cancer.

ENDRES STUDY.[128]

Nine healthy volunteers received 2.75 g EPA/day for six weeks. Provision of n-3 fatty acids decreased synthesis of interleukin 1α (IL-1α), interleukin 1β (IL-1β), and TNF-α by peripheral-blood mononuclear cells that were stimulated *in vitro* by endotoxin for at least ten weeks post-supplementation. The researchers concluded that n-3 fatty acids might inhibit cytokine production, resulting in an anti-inflammatory effect.

CAUGHEY STUDY.[136]

Caughey and colleagues demonstrated cytokine and eicosanoid modulation in 28 healthy adult men who were fed diets containing varying amounts of n-3 fatty acids. EPA supplementation was provided in the form of nine fish oil capsules per day (1.62 g EPA/day). At eight weeks, cellular EPA concentrations were significantly greater than those in baseline measurements. Elevated concentrations of EPA in mononuclear cells were coupled with a significant reduction in endotoxin-induced synthesis of IL-1 and TNF-α. Synthesis of the eicosanoids↑thromboxane B_2 and prostaglandin E_2↑was also reduced by 52% and 55%, respectively.

GOGOS STUDY.[137]

Gogos and colleagues used fish oil capsules in a randomized study of 64 people with incurable malignancies, including cancers of the breast, GI tract, lung, liver, and pancreas. None of the patients were receiving chemotherapy during the study or during the four months prior to the study. Patients were given six fish oil capsules (170 mg EPA/capsule) or a placebo three times a day. The active treatment group also received 200 mg of vitamin E daily to prevent oxidation of the n-3 fatty acids. The treatment and placebo groups were divided into two subgroups—malnourished and well-nourished. The aim of the study was to evaluate the impact of n-3 fatty acid supplementation on immunomodulation and survival.

Weight and serum proteins (albumin and transferrin) did not change in either treatment group.[137] A significant increase in the T helper/T suppressor lymphocyte ratio was seen in people in the malnourished group. However, there were no significant differences in the production of IL-1 and IL-6. Karnofsky Performance Status was significantly improved (P <0.01) in the malnourished-treated group. Survival was significantly prolonged (P <0.001) in the well-nourished people compared with the malnourished individuals. The best survival rates were found in the well-nourished supplemented group, and the worst survival rates were found in the malnourished placebo group. Most notably, supplementation with n-3 fatty acids and vitamin E resulted in a significantly increased survival rate (P <0.025) for all patients compared with placebo (Table 7).

Table 7: Summary:
Gogos study results[137]

Fish Oil Capsules (3 g EPA/day) Plus Vitamin E vs Placebo (n=64)

- Significant improvement in performance status in malnourished-treated group
- Significant increase in T helper/T suppressor lymphocyte ratio in the malnourished group
- Increased survival rate

EICOSAPENTAENOIC ACID AND WEIGHT STABILIZATION

Wigmore Study, 1996.[129] Wigmore and colleagues studied 18 people with unresectable pancreatic cancer and cancer-induced weight loss to determine the effect of fish oil on weight. Fish oil capsules were administered at a starting dose of 2 g/day and increased at weekly intervals by 2 g/day to a maximum dose of 16 g/day. The median maximum dosage over the study was 12 g/day of fish oil, which delivered 2 g/day EPA. The plasma phospholipid EPA concentration increased from undetectable levels before supplementation to a median of 5.3% (range, 3.5% to 6.2%) of the total fatty acids after one month of supplementation, confirming that the individuals were taking the supplement.

Before supplementation, individuals had a median weight loss of 2.9 kg/month. A median weight change of 0.3 kg/month was observed after a median interval of three months of supplementation. Eleven study participants gained weight, three were weight-stable, and four continued to lose weight but at a reduced rate. Their total body water did not change significantly during the study, indicating that the observed weight stabilization or gain was not attributable to fluid retention. Oral fish oil supplementation tempered weight loss and altered the progression of cachexia in this group of people with pancreatic cancer (Table 8).

Table 8
Summary: Wigmore study results[129]

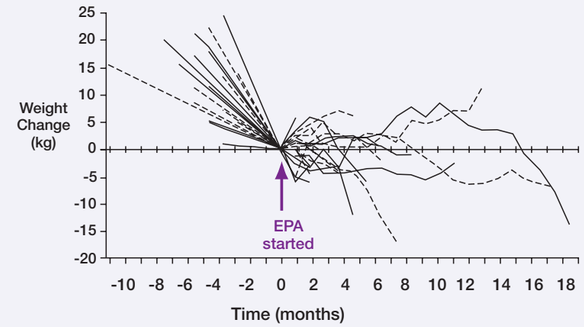
Fish Oil Capsules (2 g EPA/day) in Pancreatic Cancer Patients (n =18)

- Increased plasma phospholipid EPA at one month
- Progression of weight loss altered; median weight change of 0.3 kg/month after a median three months of supplementation (weight stabilization)
- No change in total body water

Wigmore Study, 2000.[127] In a subsequent study, Wigmore and colleagues evaluated the effect of highly purified EPA (500 mg EPA/capsule) supplementation in weight-losing people with advanced pancreatic cancer who were not receiving treatment. In this 12-week study, 26 study participants were given daily EPA supplementation starting at 1 g/day for the first week and increasing to a maximum of 6 g/day from week four to the end of the study. Before supplementation, these individuals had been losing a median of 2.0 kg/month and had lost a median of 13% of their usual body weight.

After one month of EPA supplementation, 16 study participants had become weight-stable or had gained some weight. A median weight gain of 0.5 kg/month was observed after four weeks of supplementation. There were no significant changes in total body water, and the percentage of people with an elevated CRP did not increase. As in the previous study conducted by Wigmore et al, highly purified EPA stabilized weight in people with pancreatic cancer and tempered the progression of weight loss (Figure 9). However, increasing the maximum daily dose of EPA from 2 g to 6 g did not appear to enhance the anticachectic effects.

Figure 9
Weight changes in pancreatic cancer patients (n = 26) who were given EPA[127]



In summary, use of cell, animal, and human studies support the concept that dietary EPA lessens effects of pro-inflammatory cytokines and PIF, thus attenuating APPR, hypermetabolism, and protein degradation. As a result, researchers hypothesized that providing EPA in combination with supplemental energy and protein would result in weight gain rather than just weight stabilization in otherwise weight-losing patients with cancer. This hypothesis led to the rational development of a nutritional formula that is now marketed as ProSure®.

PROSURE® AS THERAPEUTIC NUTRITION

ProSure® is a high-protein, energy-dense, low-fat oral supplement that is enriched with EPA. It is designed to meet the specific nutritional needs of people who experience weight loss associated with cancer or who are at risk for this complication.

Each 240-mL serving of ProSure® contains 1.1 g EPA; two servings a day are thus recommended to provide the optimal level of 2.2 g of EPA for people with weight loss induced by metabolic abnormalities associated with cancer.

STUDIES OF PROSURE®

Two key studies initially evaluated the efficacy of ProSure® treatment in weight-losing patients with cancer:

- A pilot study
- A prospective, randomized, controlled trial

Researchers hypothesized that providing EPA in combination with supplemental energy and protein would result in weight gain, rather than just weight stabilization, in otherwise weight-losing patients with cancer.

Patients with pancreatic cancer were chosen for the study population in these studies as a study model for cancer induced weight loss. People with pancreatic cancer experience rapid, severe weight loss, often between 15% and 20% of body weight by the time of diagnosis. Prognosis in this population is poor (survival less than six months) due to the aggressive nature of the tumor. Similar results are expected in patients with cancer-induced weight loss due to other types of cancer.

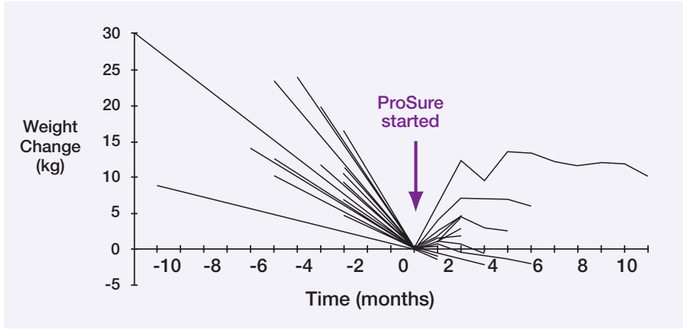
PILOT STUDY

In a pilot study conducted by Barber and colleagues,[15, 16] ProSure® was given to 20 weight-losing patients with advanced pancreatic cancer. The median weight loss in this group was 2.9 kg/month (6.4 lb/month) before enrollment. Study participants were asked to consume two servings (240 mL/serving) of ProSure® per day for seven weeks. Weight, body composition, and functional status data were collected at baseline, three weeks, and seven weeks. Resting energy expenditure (REE), food intake, and QOL data were collected at baseline and three weeks only.

Results. The results of this pilot study are summarized as follows:

- **Good compliance**. Median consumption of ProSure® was 1.9 servings/day.
- **Weight gain (Figure 10)**
  - three weeks (median 1.0 kg [2.2 lb]) (*P* =0.024)
  - seven weeks (median 2.0 kg [4.4 lb]) (*P* =0.028)

Figure 10
Weight change in pancreatic cancer patients who were given ProSure®[15]



- **Increased lean body mass.** Statistically significant increases in lean body mass at both three and seven weeks. Weight gain was predominantly lean body mass (95% of total weight gain), not fat or water.
- **Increased functional status.** Statistically significant increase in functional status (Karnofsky Performance Status) at both three and seven weeks. There was an improvement in the ability to function independently and carry out normal activities of daily living.

Conclusion

ProSure® supplementation produced statistically significant gains in weight and lean body mass in patients with pancreatic cancer who were experiencing cancer-induced weight loss. Appetite, dietary intake, and functional status also improved.

- **Increased appetite and dietary intake**. Statistically significant improvements in appetite and dietary intake at three weeks. Participants consumed a median additional 372 kcal/day at three weeks. They did not substitute ProSure® for their usual food intake. Therefore, ProSure® supplemented their diet and increased caloric intake.
- **Decreased resting energy expenditure (REE).** Statistically significant reduction in REE or resting metabolic rate (RMR) at three weeks.
- **Tolerance.** Well tolerated with no major side effects.
- **Decreased interleukin production.** After three weeks of supplementation, there was a significant decrease in IL-6 production (from median 16.5 to 13.7 ng/mL, *P* =0.0015) and a trend for a decrease in IL-1 production (*P* =0.068).[16]
- **Decreased cortisol/insulin ratio.** The cortisol/insulin ratio was significantly decreased at three weeks, indicating lowered "stress" and a greater likelihood for anabolism than for catabolism.[16]
- **Decreased PIF.** At the beginning of the study, PIF was present in the urine of 88% of people with pancreatic cancer; PIF was found in the urine of only 40% of people after taking ProSure® for three weeks. The decreased level of PIF in the urine suggests that ProSure® has the potential to prevent loss of lean body mass.[16]

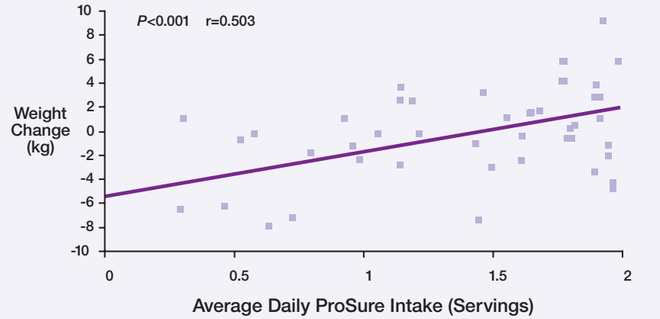
RANDOMIZED CONTROLLED TRIAL

Based on the positive results of the pilot study, Fearon and colleagues[18] conducted a larger prospective, randomized, controlled trial to confirm the findings. In this study, ProSure® and an isonitrogenous, isocaloric formula (control) were studied in 200 people with advanced pancreatic cancer. Before the study, participants were losing weight at a median rate of 3.3 kg/month (7.3 lb/month). Of the 200 participants enrolled, 95 were randomized to the experimental group that received ProSure® and 105 to the control group. Study participants were asked to drink two servings/day (240 mL/serving) of ProSure® or the control supplement for eight weeks. Weight, lean body mass, dietary intake, and quality of life (EORTC QLQ-C30 and EQ-5D) were measured.

Results

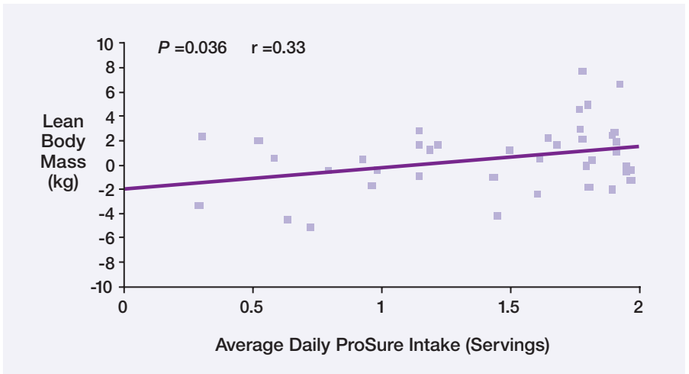
- **Completion.** A total of 110 people completed the eight-week study; 90 people did not complete the study because of disease progression and death.
- **Weight.** Weight of people in both groups stabilized at four and eight weeks. ProSure® intake was positively correlated with increased weight (*P* < 0.001, r = 0.50; Figure 11).

Figure 11
Increased daily intake of ProSure® was positively correlated with increased body weight at eight weeks.[18]



- **Lean body mass**. ProSure® intake was positively correlated with increased lean body mass (r =0.33, *P* =0.036; Figure 12). There was no such correlation with the control group (i.e., people who consumed the isocaloric) isonitrogenous product.)
- **Dietary intake**. People consuming ProSure® had a significant increase in total (meal plus supplement) energy and protein intake after eight weeks. There was no increase in the control group.

Figure 12
Increased daily intake of ProSure® was positively correlated with increased lean body mass at eight weeks[18]



- **Quality of life (QOL) and grip strength.** ProSure® intake positively correlated with QOL measured by the EQ-5D index (r =0.37, *P* =0.01; Figure 13), but there was no correlation in the control group.[18] Weight gain in the ProSure® group also correlated with improvements in other measures of QOL and with measures of physical function: EQ-$5D_{index}$ (r =0.46, *P* =0.001), EQ-$5D_{vas}$ (r =0.38, *P* =0.01), physical functioning domain of QLQ-C30 (r =0.33, *P* =0.022; Figure 14), and grip strength (r =0.38, *P* =0.009). There was no correlation in the control group.[18, 35]

Figure 13
Effect of weight change on EQ5D Score[35]

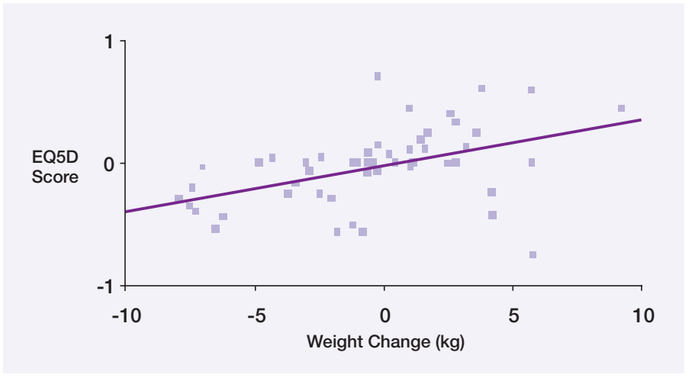
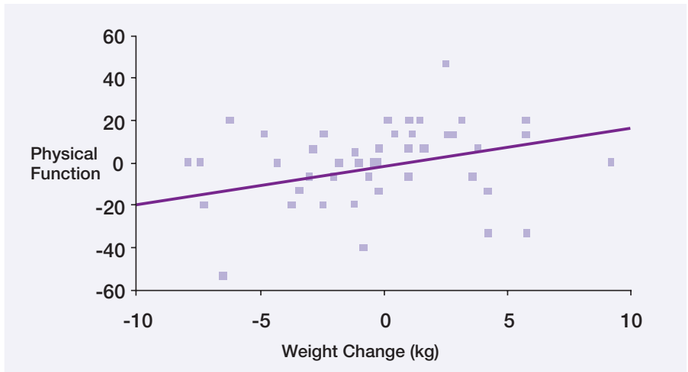


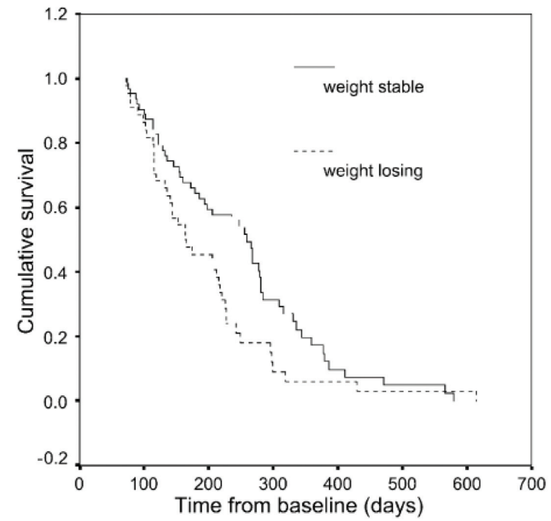
Figure 14
Effect of weight change on QOL-C30 physical function score[35]



DAVIDSON 2004[31]: PROSURE® IN PATIENTS WITH UNRESECTABLE PANCREATIC CANCER

Davidson and colleagues performed a post hoc analysis of data from 107 patients who were enrolled in the Fearon 2003[18] trial. Patients were included in the post hoc analysis if weight data was available for both baseline and week eight. Patients with weight stabilization survived longer from baseline (log rank test 5.53, *P* = 0.019) (Figure 15). In addition, quality of life scores were higher (*P* = 0.037) and mean energy intake was greater (*P* < 0.001) at week eight compared to patients who continued to lose weight. In weight-losing patients with unresectable pancreatic cancer, weight stablization over an eight-week period was associated with improved survival duration and quality of life.

Figure 15
Improved survival in patients with weight stabilization



Conclusion

ProSure®-consuming patients with pancreatic cancer experienced an increase in PAL; they improved from a baseline PAL of 1.2-1.3 (confined to bed) to a near-normal sedentary level (PAL=1.5).

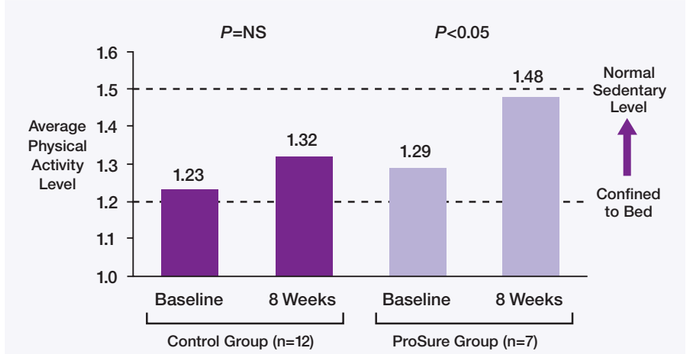
PHYSICAL ACTIVITY STUDY

Moses and colleagues[32, 138] studied the effect of ProSure® on physical activity level (PAL) in 19 weight-losing patients with pancreatic cancer. Study participants were asked to consume two cans/day of supplement (control, n=12; ProSure®, n=7) over an interval of eight weeks. Total energy expenditure (TEE) was measured at baseline (within the first 14 days of the study) and again between six and eight weeks using the doubly-labeled water technique. Resting energy expenditure (REE) was measured by indirect calorimetry, and PAL was calculated by the formula PAL=TEE/REE.

Results. The results of the Moses study are as follows:

- **PAL**. There was a statistically significant (P <0.05) increase from baseline PAL in the ProSure® group (Figure 16).[32, 138] There was no significant PAL change in the control group; most patients remained confined to bed. This significant increase in PAL parallels the significantly increased Karnofsky Performance Status previously reported for pancreatic cancer patients who received ProSure® nutrition.[15]

Figure 16
Change in PAL for patients treated with ProSure® versus control



PROSURE® CLINICAL STUDIES

STUDIES IN PATIENTS WITH LUNG CANCER

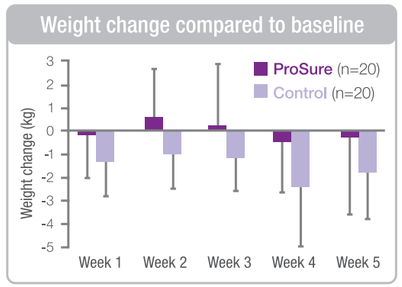
Use of an oral nutritional supplement enriched with EPA has been shown to attenuate the proinflammatory response through a decrease in IL-6, IL-8, IL-10, TNF-α and C-reactive protein, and an increase in the negative acute phase proteins albumin, prealbumin, and transferrin.

Guarcello 2006[23]: ProSure® in patients with lung cancer. A study by Guarcello evaluated weight losing patients with lung cancer who were scheduled to undergo chemotherapy. Patients (n=46) were randomized to supplement their usual oral diet with either two cans per day of ProSure® or an isocaloric, isonitrogenous nutrition supplement without EPA. Over the two-month study interval when chemotherapy was administered, only patients who received ProSure® showed significant increases in body weight (at 30 days, + 0.9 kg, $P < 0.05$), energy and protein intakes, appetite, and quality of life (Table 7). In addition, levels of negative acute phase proteins were significantly increased at 30 days (prealbumin + 3, $P < 0.05$; transferrin + 26, $P < 0.05$), while levels of inflammatory marker C-reactive protein were decreased in patients who consumed ProSure®.

Table 7
ProSure® in patients with lung cancer

	EPA-ONS (n=26)			CONTROL (n=20)		
	Baseline	**30 days**	**60 days**	**Baseline**	**30 days**	**60 days**
Body weight, kg	57.7	58.6	58.6	59.1	57	59.1
Functional QOL EORTC QLQ-C30 FS	64.4	82.2	77.7	62.2	72.4	72.2

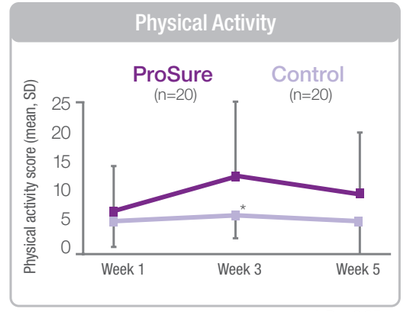
van der Meij 2010,[22] 2012[36]: ProSure® in patients with non-small cell lung carcinoma. van der Meij and colleagues conducted a double-blind, randomized, controlled trial in patients with stage III non-small cell lung carcinoma (n=40). Patients were randomized to receive two servings a day of either ProSure® nutrition supplement or an isocaloric control supplement (Ensure) during five weeks of chemo-radiotherapy.



Results

- **Weight**. Patients consuming ProSure® had better weight maintenance than the control group after week one, two, and four (1.1 kg, $P = 0.07$; 1.3 kg, $P = 0.02$; and 1.7 kg, $P = 0.04$, respectively).[22]
- **Fat-free mass.** Patients consuming ProSure® had better fat-free mass (FFM) maintenance after week three and five than the control group (1.5 kg, $P = 0.05$ and 1.9 kg, $P = 0.02$, respectively).[22]
- **Dietary intake**. Energy and protein intake was higher in the ProSure® group compared to the control group after week four; 2456 kJ/24 hours, $P = 0.03$ and 25.0 g, $P = 0.01$, respectively.[22]
- **Quality of life**. After five weeks, the ProSure® group had significantly higher scores on the quality of life parameters, physical and cognitive function, global health status, and social function (as measured by EORTC- QLQ-C30) than the control group. Karnofsky Performance Status was also higher in the ProSure® group after three weeks compared to the control group.[36]

- **Physical activity (measured with a physical activity monitor (PAM) accelerometer)**. Tended to be higher in the ProSure® group than the control group after three and five weeks.[36]



* $P < 0.05$

These findings underscore the beneficial effects of high-protein, calorically-dense, low-fat nutrition with EPA (ProSure®) on nutritional status and physical function in patients with non-small cell lung carcinoma undergoing chemo-radiotherapy.

Sanchez-Lara 2012[30]: ProSure® in patients with advanced non-small cell lung cancer (NSCLC). Sanchez-Lara evaluated the effect of an oral nutritional supplement (ONS) with EPA (ProSure®) on nutritional and inflammatory parameters, response and toxicity to chemotherapy, quality of life, and survival in treatment-naïve patients with advanced NSCLC. All patients received paclitaxel and cisplatin-carboplatin treatment. Patients in the experimental group (n=46) had an increase of 1.6 kg in lean body mass compared to the control group (n=46). The experimental group also had significantly increased albumin levels, energy, protein, lipid, and carbohydrate intake, and reduced serum CRP, TNF-α and Neutrophils/Lymphocytes index. Health-related quality of life parameters improved in the experimental group in global and physical scale and anorexia, while toxicity, fatigue and neuropathy decreased.[30]

STUDIES IN PATIENTS WITH HEAD AND NECK CANCER

de Luis 2005[21]: ProSure® in patients with head and neck cancers. The study by de Luis and colleagues randomized a population of patients with head and neck cancers (n=73) to receive two servings a day of a nutritional supplement—either ProSure® or an isocaloric, arginine-enriched drink—during a 12-week period of recovery from cancer surgery. From baseline to three months, patients consuming ProSure® exhibited a statistically significant increase in weight (65.5 ± 11.5 kg vs 70.4 ± 11.1 kg; $P < 0.05$), fat mass (15.4 ± 6.6 vs 18.1 ± 8.4 kg; $P < 0.05$), and tricipital skinfold (10.9 ± 4.7 vs 12.35 ± 6.1 mm; $P < 0.05$). The patients consuming the arginine-enriched drink only experienced an increase in visceral proteins.

Garcia-Almeida 2010[34]: ProSure® in patients with otolaryngeal cancer. Garcia-Almedia evaluated the effect of an oral supplement enriched with omega-3 fatty acids on inflammatory parameters and oxidative stress in 32 patients with otolaryngeal cancer who were undergoing radical radiotherapy. Oxidative stress and inflammatory parameters were significantly improved in the patients who consumed the supplement enriched with omega-3 fatty acids compared to the patients who received the standard supplement. After three months of treatment, the patients in the supplement enriched with omega-3 fatty acids group experienced:

- An increase in total antioxidant capacity ($P < 0.05$)
- An increase in glutathione peroxidase activity ($P < 0.01$)
- A decrease in lipoperoxide levels ($P < 0.05$)
- A decrease in C-reactive protein levels ($P < 0.05$)

These findings suggest that a supplement enriched with omega-3 fatty acids appears to improve oxidative stress in patients with otolaryngeal cancer treated with radiotherapy.

Weed 2011[26]: ProSure® in patients with head and neck cancer. Weed and colleagues conducted a prospective, single-arm, open-label study in patients with head and neck cancer (n = 38) experiencing unintentional weight loss of at least 5% during the preceding six months who were scheduled for surgical resection with curative intent. Patients were to consume two cans of ProSure® two weeks before surgery and continue with ProSure® during hospitalization.

Results

- **Weight**. Seventy percent (n = 27) of the patients maintained or gained weight from study entry to time of hospital admission (+ 0.71 kg; *P* = .245). Fifty-seven percent (n = 30) of the patients maintained or gained weight from study entry to hospital discharge (+ 0.66 kg; *P* = .519).
- **Lean body mass**. There was a statistically significant increase in mean lean body mass in 23 patients from study entry to hospital discharge: +3.20 kg; +7% (*P* < .001).

Data from this pilot study suggests that patients with head and neck cancer can benefit from a protein and energy dense, EPA-containing nutritional supplement before and after surgical treatment.

Chang 2011[139]: ProSure® in patients with previously untreated stage IIb-IV nasopharyngeal cancer (NPC). Patients with previously untreated stage IIb-IV nasopharyngeal cancer (NPC) who were to receive concomitant chemoradiotherapy were enrolled in this open-label, prospective, randomized trial. Fifty-nine patients were randomized to the EPA-containing nutrition supplement (ProSure®) group and 57 were in the control group. After three months, a significant difference between the groups was found in infection rates requiring hospitalization: six patients in the EPA supplement group (10.2%) vs.16 patients in the control group (28.1%), *P* = 0.014. The use of an EPA-containing supplement was found to significantly decrease the rate of hospital admission due to infection in patients with NPC who were receiving chemoradiotherapy.

STUDIES IN PATIENTS WITH GI CANCER

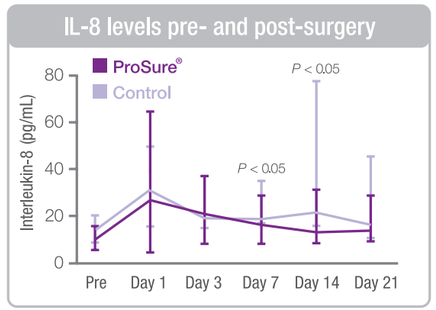
Read 2007[24]: ProSure® in patients with advanced colorectal cancer. In a prospective, open-label study by Read and colleagues, patients with advanced colorectal cancer were given ProSure® three weeks before chemotherapy began and for nine weeks during chemotherapy; n=23 patients enrolled, n=20 patients completed three weeks; and n=15 completed nine weeks. Results showed that ProSure® feeding (average daily intake 408 mL) produced a significant increase in mean weight (+2.5 kg, *P* = 0.03) at three weeks and preserved lean body mass during chemotherapy. In addition, there was a significant increase in energy levels (*P* = 0.03) during the study, while quality of life (QOL) was maintained. (Table 8)

Table 8
ProSure® in patients with advanced colorectal cancer

MARKER	BASELINE	PRE-CHEMO END WEEK THREE	DURING OR POST-CHEMO END WEEK NINE	*P* VALUE
Weight, kg	75.9 (17.0)	78.4 (17.5)	78.4 (17.4)	0.03
Lean body mass, kg	50.3 (10.7)	51.4 (10.2)	51.7 (10.6)	NS
C-reactive protein, mg/L	18.2 (13.9)	33.1 (32.6)	19.4 (17.7)	0.004 (end of week three) 0.02 (end of week nine)
QOL-overall well-being	7 (2.2)	7 (1.7)	8 (1.7)	0.05

Mean values (SD)
P values are for baseline vs. timepoint value; NS, not significant

Ryan 2009[29]: ProSure® in patients undergoing surgery for esophageal cancer. In a prospective, randomized, double-blind, controlled trial, Ryan and colleagues evaluated the effect of consuming ProSure® pre- and postoperatively in patients undergoing esophagectomy. Patients were randomly assigned to receive either ProSure® (two cans, containing a total of 2.2 g EPA per day; n=28) or an isocaloric, standard nutritional formula (n=25) for five days before and for 21 days after surgery. ProSure®-fed patients maintained lean body mass throughout the study, while patients on standard enteral nutrition lost significant amounts of muscle from the leg (0.3 kg ± 0.6; *P* = 0.05), arm (0.17 kg ± 0.3; *P* = 0.01), and trunk (1.44 kg ± 2.7; *P* = 0.03), for a total loss of 1.9 kg (± 3.7) lean body mass. In the hospital, 39% of standard-fed patients experienced severe weight loss (> 5% total body weight), but only 8% of ProSure®-fed patients showed such loss, a difference that was statistically significant (*P* = 0.03). Compared with the standard enteral nutrition fed group, the ProSure®-fed group also had a significantly (*P* < 0.05) attenuated stress response to surgery based on measures of IL-8, IL-10, and TNF-α.



IL-8 levels were significantly lower on postoperative days 7 and 14 in the ProSure® group compared to the control group.

In a recent prospective, randomized, controlled study in patients with colorectal cancer, patients who consumed ProSure® gained significantly more weight and were able to tolerate chemotherapy better than patients in the control group.

Trabal 2010[27]: ProSure® in patients with colorectal cancer. Trabal et al conducted a prospective, randomized, controlled, open-label pilot study in patients with stage IV colorectal cancer who were to receive first line chemotherapy. Patients were randomized to ProSure® and dietary counseling (n = 6) or dietary counseling alone (n = 7). At three months, patients in the ProSure® group gained significantly more weight compared to the control group (4.94 kg vs. -1.17 kg; *P* = .045). After three months a statistically significant difference was found between the groups for the social function scale (16.67 vs. -13.89; *P* = .038). Both groups had a decrease in physical function (-4 vs. 15.56; *P* = not significant); however, only the control had a worsening over ten points, which is considered clinically meaningful. The ProSure® group experienced an improvement in role function (13.33 vs. 2.78; *P* = not significant). Changes over ten points were also found with the control group experiencing more fatigue (-4.44 vs. 11.11; *P* = not significant) and pain (-10 vs. 2.78; *P* = not significant). There were zero delays in chemotherapy in the supplement group compared to four in the control group. These results suggest that intervention with an EPA-enriched nutritional supplement with dietary counseling appears to have a positive effect on weight maintenance, health-related quality of life and chemotherapy tolerability in patients with advanced colorectal cancer.

Kilic 2012[37]: ProSure® in patients with advanced rectal cancer. Kilic and colleagues prospectively studied 80 patients with advanced rectal cancer who were undergoing preoperative chemoradiotherapy to evaluate the effect of ProSure® (n = 40) on toxicity, quality of life (QOL), tumor response, and prognosis compared to patients in the control group (n = 40). Patients in the ProSure® group experienced less diarrhea (Grade two or higher) than the control group (55% vs. 80%; *P* = 0.03) and less GI toxicity than the control group (40% vs. 92%; *P* = 0.001). At the end of chemoradiotherapy, there were significant differences between the groups in favor of ProSure® in QOL scores in the functional and symptom scales. Pathological complete response rate was achieved in 37% of the ProSure® group compared to 20% in the control group. Statistically significant differences were found in disease-free survival and overall survival in favor of the ProSure® group (*P* < 0.001).

STUDIES IN PATIENTS WITH PANCREATIC CANCER

Barber 1999[33]: ProSure® in patients with pancreatic cancer. Barber and colleagues evaluated the effect of a fish-oil enriched nutritional supplement on the levels of individual acute-phase proteins in weight-losing patients with advanced pancreatic cancer. Thirty-six patients were enrolled: 18 in the supplement group and 18 in the supportive care group.

Results

- **Acute phase proteins**. A significant increase in negative acute phase proteins (albumin, prealbumin, and transferrin) (+1.32 g/L) was observed in patients receiving the fish-oil enriched nutritional supplement ($P = 0.048$) compared with a significant decrease (-2.44 g/L) in the patients receiving supportive care. The difference between the two groups was highly significant ($P = 0.0012$).
- **Weight**. Although not a primary outcome, a positive effect on weight was observed after four weeks in the patients receiving the fish-oil enriched nutritional supplement (median change in weight = +1.0 kg) compared to the patients receiving supportive care (median change in weight = -2.8 kg).

These results suggest that a fish-oil enriched nutritional supplement may help stabilize the acute-phase protein response thereby helping to reduce wasting in patients with advanced pancreatic cancer.

Barber 2000[17]: ProSure® in patients with pancreatic cancer. Barber and colleagues enrolled weight-losing, non-diabetic patients with unresectable pancreatic adenocarcinoma and healthy, weight stable controls in this prospective, single-center, single-arm study to evaluate the effect on the metabolic response to feeding after consuming a fish-oil enriched nutritional supplement for three weeks. After three weeks of consuming the fish-oil enriched nutritional supplement, patients experienced:

- Median weight gain of 1.0 kg (-0.25 to 1.75) ($P < 0.05$ compared with baseline)
- Median increase in lean body mass of 0.75 kg (0.1-1.6) ($P < 0.05$)
- No effect on fat mass, 0.0 kg (-0.6 to 0.9)
- Resting energy expenditure rose significantly in response to feeding (9.6%) and was no different from baseline healthy control values.

STUDIES IN PATIENTS WITH MIXED OR OTHER CANCER TYPES

Jatoi 2004[20]: ProSure® versus appetite stimulant megesterol acetate. Patients with incurable cancer and weight loss greater than five pounds (2.3 kg) within two months (or physician-estimated caloric intake < 20 kcal/kg weight each day; n=421) were randomized to receive either ProSure® plus placebo megestrol acetate, megestrol acetate plus an isocaloric, isonitrogenous control nutritional supplement, or ProSure® plus megestrol acetate for four weeks. Results showed that both ProSure®- and megestrol acetate-treated groups had more than one-third of patients gaining weight over the four-week course. ProSure® was as effective as megesterol acetate, and there were fewer side effects with ProSure®.

Bauer 2005[19]: Weekly counseling and use of ProSure® in patients with pancreatic or lung cancer. In a study of seven patients with pancreatic or non-small cell lung cancer, Bauer and colleagues demonstrated that nutritional intervention (weekly counseling and use of ProSure®) in addition to chemotherapy provided significant benefits. These benefits included improvements in quality of life (EORTC QLQ-C30 global scale), performance status (Karnofsky performance score), total energy and protein intake, as well as weight gain and increases in lean body mass.

Capuano 2005[25]: ProSure® in patients with cancer cachexia. Capuano and colleagues conducted a prospective, single-arm study in 22 patients with cancer cachexia to determine compliance and effects of ProSure® on body mass index (BMI), body weight, ECOG performance status, prealbumin, and retinol binding protein. After four weeks, a positive correlation was observed with supplement intake and both weight gain, 3 kg ± 1 (range 2-four kg) and improvement in performance status.

Çoker 2010[140]: ProSure® in patients with periampullary carcinoma. Çoker and colleagues evaluated the role of early enteral feeding and an EPA enriched diet during the postoperative period in patients undergoing elective surgery for periampullary carcinoma. Two hundred twenty-eight patients were enrolled, with 128 patients in the fast track rehabilitation after surgery with EPA enriched supplement (ProSure®) group and 100 patients in the conventional treatment group. Patients in the fast track group experienced:

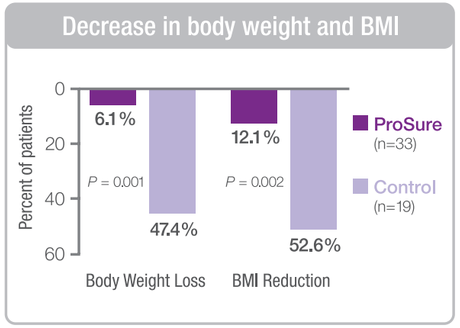
- Significantly faster resumption of bowel function (4.1 ± 0.3 days vs. 6.3 ± 0.7 days)
- Significantly shorter postoperative hospital length of stay (6.7 ± 0.8 days vs. 13.1 ± 0.5 days)
- Less postoperative weight loss at two months (6.5% vs. 13.6%)

These results suggest that fast track rehabilitation after surgery with an EPA enriched supplement can benefit high-risk patients undergoing elective surgery for periampullary cancer.

Voss 2012:[28] ProSure® in weight-losing patients with various types of solid tumors. The effect of ProSure® on weight, inflammatory blood markers, compliance, and quality of life was evaluated in weight-losing patients receiving treatment for various types of solid tumors. Patients were enrolled if they had > 5% pre-illness weight loss during the previous six months. Anticancer treatment included chemotherapy, radiotherapy, surgery, or other or no treatment. After four months of consuming ProSure®, weight was found to stabilize. Inflammation improved as demonstrated by a significant decrease in CRP ($P = 0.01$) and an increase in serum albumin ($P < 0.01$). Intake of > 1.5 containers/day was noted in 77%, 75%, and 69% of the patients after month two, three, and four, respectively, which demonstrates good compliance over time.

STUDY OF PROSURE® IN CHILDREN WITH CANCER

Bayram 2008[38]: ProSure® in children receiving chemotherapy for cancer. A study by Bayram et al evaluated the effect of ProSure® on cancer-related weight loss in children who were undergoing chemotherapy. The study included 52 children with leukemia or solid tumors who were randomized to receive ProSure® (n=33) or control nutrition (n=19); the mean age of the children was 7.5 years. ProSure® (or control supplement) was recommended at two servings per day (morning, evening) in addition to usual food. Weight changes, body mass index (BMI), and tolerance were monitored for three months, with a subset of patients followed an additional six months. After three months, only 6.1% of children in the ProSure® group lost weight, compared to 47.4% of children in the control group ($P = 0.001$). Similarly, 12.1% of the children in the ProSure® group had a lowered BMI, compared to 52.6% of children in the control group ($P = 0.002$). These differences were associated with a higher rate of cancer remission in the ProSure® group compared to the control group (87.9% vs 63.2%, $P = 0.036$).



SUMMARY OF PROSURE® CLINICAL STUDY RESULTS

Clinical studies in people with cancer have shown that drinking ProSure® daily as part of overall care helps:

- Promote weight gain[15-28]
- Build or maintain lean body mass[15,17-19, 22, 24, 26, 29, 30]
- Improve appetite and dietary intake[15, 18, 19, 22, 23, 30-32]
- Attenuate the proinflammatory response[16,23, 24, 28-30, 33, 34]

ProSure® is also associated with:

- Increased strength in those who gained weight[35]
- Improved physical activity[15, 32, 36]
- Improved quality of life[18, 19, 23, 24, 30, 31, 35-37]
- Reduced treatment interruptions/toxicities[27, 30, 37, 38]

FEATURES AND BENEFITS OF PROSURE®

ProSure® is a therapeutic nutrition product specifically designed for people at risk for or experiencing cancer-induced weight loss to help restore normal metabolism and promote weight gain, help build lean body mass, and improve QOL. ProSure® contains a unique blend of prebiotic fiber to help promote digestive tract health with EPA from fish oil and antioxidants to support immune health. ProSure® has many features that provide specific nutritional benefits for people with cancer (Table 9).

Table 9
ProSure® features and benefits

FEATURE	BENEFIT
Clinically demonstrated efficacy	Clinical studies in people with cancer have shown that drinking ProSure® daily as part of overall care helps: • Promote weight gain[15-28] • Build or maintain lean body mass[15,17-19, 22, 24, 26, 29, 30] • Improve appetite and dietary intake[15, 18, 19, 22, 23, 30-32] • Attenuate the proinflammatory response[16,23, 24, 28-30, 33, 34] ProSure® is also associated with: • Increased strength in those who gained weight[35] • Improved physical activity[15, 32, 36] • Improved quality of life[18, 19, 23, 24, 30, 31, 35-37] • Reduced treatment interruptions/toxicities[27, 30, 37, 38]
Contains 1.1 g EPA/240 mL	EPA, an omega-3 fatty acid derived from fish oil, modulates the metabolic abnormalities that are associated with cancer-induced weight loss Helps stabilize weight and lean body mass
High protein–21% of total calories (16 g/240 mL)	Supplies a generous amount of high-quality protein, which helps build lean body mass in people with cancer
Energy dense–1.27 kcal/mL (300 Cal/240 mL)	Provides concentrated nutrition in a small volume for people with decreased appetite and food intake Helps meet the increased caloric needs of people with cancer
Low in fat–18% of total calories	Low fat diets are often recommended to help reduce treatment-related side effects such as delayed gastric emptying and early satiety that can be associated with higher fat diets Low fat diets also help promote better tolerance in cancer patients who commonly experience fat malabsorption and diarrhea
Contains medium-chain triglycerides (MCT)	MCT are an easily digested, readily absorbed source of fat
Optimal n-6 to n-3 ratio (0.3 to 1.0)	Developed and studied for optimal composition of fatty acids that can help normalize metabolism in people with cancer-induced weight loss
Contains scFOS, 2.6 g/240 mL	Helps manage diarrhea associated with chemotherapy or radiation therapy and helps relieve constipation associated with pain medications
Helps with patient compliance	Only two 240-mL servings per day are needed for benefits
Contains 28 vitamins and minerals and other nutrients	Helps meet the needs of people with cancer who often have a deficient intake of vitamins and minerals
Taste-tested flavors	Was developed to meet the taste preferences of people with cancer Available in five flavors—banana, orange, vanilla, chocolate and café latte—to help prevent flavor fatigue
Less sweet	Tailored for the preferences of people with cancer who often have an aversion to highly sweetened food tastes
Lactose- and gluten-free	Can be consumed by people with lactose- and gluten-intolerance

EPA = eicosapentaenoic acid, an omega-3 fatty acid scFOS = short-chain fructooligosaccharides, a prebiotic fiber, in liquid ProSure®

INDICATIONS FOR USE

ProSure® is specifically formulated to address the nutritional needs of people with cancer-induced weight loss or who are at risk for developing this complication.

TASTE-TESTED FLAVOR

People with cancer often develop taste and smell alterations that can influence dietary intake. These alterations may result from the disease itself and/or from treatment.[141-144] Cancer patients commonly report intolerance to sweet-tasting foods and beverages. The result is that many cannot consume adequate nutrients to meet their increased nutritional needs. For oral nutritional supplements to be effective in increasing dietary intake, they must be acceptable and palatable to the person with cancer to ensure continued compliance. One reason for noncompliance may be that the flavor systems for these supplements are too sweet and not designed specifically for people with cancer.

ProSure® flavors were specifically developed to meet the preferences of people with cancer. In all, 150 flavors were screened, and eight were tested in a study including more than 500 people with cancer in seven countries.[145] The ProSure® flavors (banana, orange, and vanilla) were selected on the basis of this international sensory research, providing assurance to clinicians that the product will be acceptable to their patients with cancer. Banana was the number-one flavor selected by people with cancer across the world.

NUTRITIONAL CHARACTERISTICS

Caloric Density. ProSure® is calorically dense—1.27 Cal/mL, 300 Cal/240 mL. This caloric concentration benefits people with cancer who often have a poor appetite and limited food intake but who also have high calorie needs. The higher caloric density minimizes the volume needed to provide adequate nutritional supplementation.

Caloric Distribution. Table 10 lists the macronutrient composition of ProSure®.

Table 10
Macronutrient composition of ProSure®*

NUTRIENT	% TOTAL CALORIES	g/240 ML
Protein	21	16
Carbohydrate	61	44
Fat	18	6

* ProSure® also contains 191 g water per 240 mL.

Protein.
The protein sources in ProSure® are:

- 47.5% sodium caseinate
- 47.5% hydrolyzed sodium caseinate
- 5% whey protein concentrate

Each 240-mL serving provides 16 g of protein. ProSure® is a source of high-quality protein that is required to promote anabolism and to help build lean body mass in people with cancer-induced weight loss. The total calorie/nitrogen ratio is 117:1. A ratio of 100:1 to 150:1 is appropriate to meet the needs of stressed individuals.[146]

Carbohydrate.

The carbohydrate sources in ProSure® are:

- 62.7% corn syrup solids
- 10.0% sucrose
- 15.7% maltodextrin

The carbohydrate system in ProSure® provides both readily digestible carbohydrate for energy and nondigestible fiber for digestive-tract health. ProSure® has low-sucrose content and lacks artificial sweeteners, thus affording a taste that is less sweet than other nutritional supplements. This taste is a benefit for people with cancer who prefer food and beverages that are not highly sweet.

Fiber.

The fiber sources in ProSure® are:

- 6.0% short-chain fructooligosaccharide (scFOS) (in liquid ProSure®)
- 4.7% gum arabic
- 0.9% soy polysaccharide

ProSure® contains 5 g of fiber—of which 2.6 g is scFOS—per 240-mL serving. scFOS, a source of prebiotic fiber, is fermented in the colon to short-chain fatty acids. These short-chain fatty acids create an acidic environment in the colon, thus inhibiting growth of harmful bacteria such as *Clostridium difficile* in at-risk patients (8 g/day recommended).[147-149] Serving as a preferred energy source for cells lining the colon, short-chain fatty acids also help maintain GI tract integrity. In addition, short-chain fatty acids enhance water and electrolyte absorption in the colon,[150, 151] which is important in the management of diarrhea.

Fat.

The fat source in ProSure® is a patented oil blend (Table 11) that contains:

- 65% refined, deodorized marine oil
- 16.2% medium-chain triglycerides
- 9.3% canola oil
- 5.5% soy oil
- 4% soy lecithin

Table 11
Fat Profile of ProSure®

TYPE OF FAT	PER 240 ML
Polyunsaturated fatty acids	2.7 g
Monounsaturated fatty acids	1.3 g
Saturated fatty acids	2.0 g
Omega-6: omega-3 ratio	0.3:1
Total fat	6.0 g

The EPA content of ProSure® is 1.1 g/240-mL serving, so two servings provide 2.2 g of EPA per day.

ProSure® is lower in fat than standard medical nutritional products because many people with cancer have difficulty digesting and tolerating fats. The total fat content is 6 g per 240 mL serving. This relatively low fat content may help prevent delayed gastric emptying and early satiety.[152] Medium-chain triglycerides are helpful if fat absorption has been altered as a result of cancer treatment. They are a source of easily absorbed fat.

ProSure® contains the omega-3 fatty acid EPA from highly refined and deodorized marine oil. EPA helps down-regulate the inflammatory response associated with factors produced by the tumor that cause weight loss.[125-127] It is found naturally in deep-sea oily fish (e.g., salmon, mackerel, herring, sardines, and tuna).

Vitamins and Minerals. ProSure® contains 28 key vitamins, minerals, and other nutrients to help counter potential deficiencies (Table 12). People with cancer, especially those undergoing therapy, often have a reduced intake of many important nutrients.[153-155]

Table 12
Vitamin and Mineral Content of ProSure®

VITAMIN/MINERAL	PER 100 ML	PER 240 ML	% PRI[a]	% DRI[b]
Vitamin A[c]				
mcg RE	205	492	70	55
IU	1150	2760	—	—
Vitamin D				
mcg	1.7	4.1	100	27
IU	68	163	—	—
Vitamin E				
mg αTE	20	48	*	320
IU	30	72	—	—
Vitamin K, mcg	10	24	—	20
Vitamin C, mg	43	103	229	114
Folic Acid, mcg	169	406	203	102
Thiamin, mg	0.25	0.60	50	50
Riboflavin, mg	0.29	0.70	44	54
Vitamin B_6, mg	0.34	0.82	55	48
Vitamin B_{12}, mcg	0.50	1.2	86	50
Niacin, mg NE	2.5	6.0	33	38
Pantothenic Acid, mg	1.1	2.6	87	52
Biotin, mcg	5.0	12	80	40
Choline, mg	51	122	—	22
Minerals				
Sodium, mg	150	360	63	—
Potassium, mg	200	480	15	—
Chloride, mg	152	365	—	—
Calcium, mg	148	355	51	30
Phosphorus, mg	105	252	46	36
Magnesium, mg	42	101	67	24
Iron, mg	1.7	4.1	46	51
Zinc, mg	2.5	6.0	63	55
Manganese, mg	0.42	1.0	100	43
Copper, mcg	230	552	50	61
Iodine, mcg	16	38	29	25
Selenium, mcg	7.9	19	35	35
Chromium, mcg	10	24	—	69
Molybdenum, mcg	14	34	—	76

[a] Population Reference Intake, European standard
[b] Dietary Reference Intake, American standard
[c] Includes β-carotene: 70 mcg RE (700 IU) per 100 mL and 168 mcg RE (1680 IU) per 240 mL
* PRI based on daily polyunsaturated fatty acid (PUFA) intake

Osmolality/Osmolarity. The osmolality of ProSure® is 599 mOsm/kg H_2O; the osmolarity is 474 mOsm/L.

Renal Solute Load. The renal solute load of ProSure® is 538 mOsm/L.

Water. ProSure® contains 191 g of water per 240-mL serving. Because water requirements vary among people and in the same person over time, fluid intake should be monitored frequently and adjusted as necessary.

RECOMMENDATIONS FOR USE OF PROSURE®

DAILY CONSUMPTION OF PROSURE®

People who are experiencing cancer-induced weight loss or who are at risk of this complication may benefit from two 240-mL servings of ProSure® per day in addition to a regular diet. Clinical studies have shown that two servings of ProSure® (2.2 grams of EPA) address the metabolic changes seen in people with cancer-induced weight loss, and promote a gain in weight and lean body mass. ProSure® should be used for a minimum of three weeks to obtain benefits.

STARTING PROSURE®

The recommended daily intake of ProSure® is two 240-mL servings per day. ProSure® is usually served chilled. The supplement should be vigorously shaken and is best if consumed directly from a covered container through a straw. ProSure® should be consumed in the place of other low-calorie beverages, such as coffee and tea. Unused portions should be covered and refrigerated for consumption within 48 hours. Recipes that use ProSure® can be obtained at **www.prosure.com.**

As with any oral supplement, patients who previously had little or no oral intake may prefer to begin supplementation with one-half serving, working their way up to two servings per day.

PROSURE® IN A TUBE-FEEDING REGIMEN

ProSure® is available in 240-mL tetras or 500 mL ready-to-hang bottles. In a tube-feeding regimen, two 240-mL servings or one 500 mL bottle of ProSure® each day will provide 600 Cal and 32 g of protein, in addition to the recommended level of 2.2 g of EPA. The remaining daily calorie requirements should be provided by the most appropriate standard tube-feeding product.

For more information about ProSure®, visit **www.prosure.com**.

SUMMARY AND CONCLUSIONS

People with cancer often experience weight loss along with a loss of quality of life—conditions that reach far beyond the battle against malignant cell growth. Unintended weight loss may be the first symptom noticed by a patient with cancer, but weight loss is just one aspect of a more complicated condition known as cancer cachexia. Cachexia may also include loss of appetite, muscle loss, decreased strength, and physical and mental fatigue. Such impairments may in turn lead to loss of mobility, feelings of social isolation, and depression.

PROSURE® USAGE

ProSure® is therapeutic nutrition specifically designed for people with cancer who are experiencing or are at risk for weight loss. ProSure® is a high-protein, energy-dense, low-fat formulation, enriched with the omega-3 fatty acid, EPA. When used as part of overall care, ProSure® has been clinically shown to promote weight gain, build muscle, enhance physical activity, improve quality of life, and increase strength in those who gained weight. ProSure® has also been shown to attenuate the proinflammatory response that is associated with cancer cachexia.

ProSure® is:

- For oral use in addition to the daily diet
- Recommended at two servings per day
- Not intended as sole-source nutrition, but may be given up to 500 mL through feeding tube per day

PROSURE® FEATURES

ProSure®:

- Is demonstrated clinically to help build lean body mass, promote weight gain, enhance physical activity, and improve strength and quality of life in those who gained weight
- Contains 1.1 grams of EPA per serving to help build lean body mass, promote weight gain, enhance physical activity, improve quality of life, and increase strength in people who gained weight
- Includes 21% of calories as protein to help build lean body mass
- Provides 300 calories per serving to provide energy in a small volume
- Contains short-chain FOS to help manage diarrhea associated with cancer treatments (e.g., chemotherapy or radiation) and helps relieve constipation associated with pain medications
- Contains an omega-6 to omega-3 ratio of 0.3:1.0
- Provides approximately seven grams of sucrose per serving, which is well suited for cancer patients who prefer a less sweet taste
- Can be consumed by people with lactose or gluten intolerance

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