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Perioperative Immunonutrition in Head and Neck Cancer: A Feasibility Study

Mary Agnes Smith McCarthy

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Abstract

Perioperative Immunonutrition in Head and Neck Cancer: A Feasibility Study

Mary Agnes Smith McCarthy

Chair of the Supervisory Committee:
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Problem: Head and neck cancer (HNCA) has one of the highest associated mortality rates of all cancers. Immune-modulating nutrition (IMN) support before and after surgery has the potential to promote host defense, antitumor activities, and wound healing.

Aims: The aim of this study is to establish the feasibility of providing perioperative IMN support to HNCA patients in a regional referral center. Recent studies have demonstrated that perioperative IMN support results in enhanced cell-mediated immunity, decreased infectious complications, and shortened postoperative hospital stay. Secondary aims will examine nutritional, immunologic, and wound healing outcomes.

Design: This pilot study uses a prospective, blinded, randomized design.

Methods: Twelve patients with HNCA received either an IMN formula (Impact Recover®/ Impact Glutamine®; TG) or a standard stress formula (Isosource 1.5®; CG) for a period of 7 days pre- and post-operatively. Nutritional outcomes, albumin and prealbumin, were measured at baseline and 4 later time points. Immunologic outcomes were measured by DTH skin testing, and TLC and lymphocyte subset counts at 5 time points. Wound healing was assessed using the ASEPSIS scoring tool and infectious complications were documented.

Results: Perioperative nutrition support was favorably accepted by patients and staff. Subjects did not vary in demographics at baseline except for c-reactive protein (CRP) levels; BMI (M=22; SD=3.8), % weight loss (M =9.1; SD=9.3), nutritional

risk (M=2.27; SD=.65), and CRP (TG 6.87 $\pm$ 8.3 vs CG 39.5 $\pm$ 13.8, p = .02). Based on diary entries the majority of patients consumed $\geq$75% of their preoperative nutritional supplement. CD56 (Natural Killer cells) demonstrated a more rapid return to baseline on POD 1 in the TG (p=.02). Wounds in the TG had less serous drainage and erythema on POD 3 (p=.05), POD 5 (p<.0001), and POD 6 (p=.01). Hospital LOS was considerably longer (TG M=5.7, CG M=14.7; p= 0.04) in the CG; feeding issues postoperatively may have contributed to this outcome. **Conclusions:** This pilot study provided crucial information regarding preoperative interventions, timing of biomarkers, and measurement of outcomes that can be used for planning a larger, multi-site, RCT of perioperative immunonutrition for any surgical population vulnerable to nutritional and immunologic compromise.

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Introduction

The international scientific literature reports that head and neck cancer is increasing all over the world, frequently affecting more women and younger individuals. The literature also indicates that 5-year overall survival remains poor at 30% to 40% (Uzcudun, Retolaza, Fernandez, Sanchez, Grande, Garcia, et al., 2002). An estimated 29,370 men and women in the U.S. alone will develop cancer of the oral cavity and pharynx in 2005 and 7,320 will die of cancer of the oral cavity and pharynx this year. Eighty-five percent of these cancers can be linked to tobacco use. People who use both tobacco and alcohol are at greater risk for developing these cancers than people who use either substance alone (Ries, Eisner, Kosary, Hankey, Miller, Clegg, et al., 2005). While rates of tobacco use in older Americans have declined in general over the past 10 years, tobacco continues to be the primary carcinogen linked to many types of cancer. Efforts to improve outcomes have incorporated promising new developments in the field of biotherapy, chemotherapy, and radiotherapy. However, despite the important role of malnutrition in the pathogenesis of cancer, nutrition care is often overlooked in this patient population. Malnutrition has been recognized as a poor prognostic indicator for cancer treatment-related morbidity and mortality in general, and it is reported to affect 30-50% of all patients with head and neck cancer (van Bokhurst de van der Schueren, Flier, & Riezebos, 1998) Impaired immunocompetence is also described as a common phenomenon in this patient group. A rapidly developing area of research is beginning to elucidate the role of specific nutrients delivered enterally in supporting the

immune system. These nutritional substrates include omega (ω)-3 polyunsaturated fatty acids (PUFA), arginine, glutamine, and ribonucleic acid (RNA)-enriched nucleotides which have demonstrated an ability to affect cell-mediated and humoral responses when given throughout the perioperative period (Ochoa, Makarenkova, & Bansal, 2004). This immune-modulating nutrition offers another mechanism to improve outcomes by enhancement of host defense and antitumor activities.

Chapter One Statement of the Problem

Head and Neck Cancer

Incidence, Epidemiology, and Pathology

Head and neck cancer accounts for 5% of all cancer diagnoses in the United States (Ries, Eisner, Kosary, Hankey, Miller, Clegg, et al., 2004). Common sites for head and neck cancer include lip, cheek, tongue, floor of mouth, pharynx, tonsils, hypopharynx, and larynx; the highest percentage of cancers occur in the oral cavity and involve the tongue. The primary pathology is squamous cell carcinoma which arises from the lining of the oral cavity in over 95% of the cases (AHNS, 2004). These cancers are subdivided into well differentiated, moderately differentiated, and poorly differentiated depending on how closely they resemble normal lining cells. The tumor may involve nearby nerves, lymph vessels, or major arteries and veins.

Head and neck cancer has one of the highest associated mortality rates of all cancers. Over one-third of its victims are expected to die from their disease within 5 years; the overall 5-year survival rate for 1995-2001 from 9 Surveillance Epidemiology and End Results (SEER) geographic areas was 59.4% with 61.1% for white men, 63.1% for white women, 34.3% for black men, and 52% for black women. Incidence rates are more than twice as high in men as in women and are greatest in men over age 50, with the median age at diagnosis being 63 years of age. The low survival rates are in part due to the

stage distribution which shows 34% of oral cavity and pharynx cancers are diagnosed with the cancer still confined to the primary site, but 51% are diagnosed after the cancer has spread to regional lymph nodes, 10% are diagnosed after the cancer has already metastasized, and for the remaining 5% staging information is unknown (Ries et al., 2004).

Evaluation and Staging

Patient care requires the expertise of a multidisciplinary team from the time of diagnosis. The head and neck surgeon, the oral surgeon, the dietitian, nurse, speech pathologist, and social worker will all have critical roles in coordinating preoperative and postoperative care. After the patient has undergone a thorough history and physical examination to include manual evaluation of the tumor site, as well as xrays, a computerized tomography scan, and possibly a magnetic resonance imaging (MRI) study, the physician will perform a biopsy of the tumor to determine accurate staging. Staging is a well-defined method of describing the exact characteristics of the tumor for a specific patient. This assists the surgeon with formulating a definitive plan for treatment and predicts how successful therapy will be. There are three categories used to describe the tumor: T (tumor), N (lymph node involvement), and M (metastasis). This is referred to as the TNM classification system. Tumors of the oral cavity are described by their size. Tumors less than 2 centimeters (cm) are called T1. Tumors greater than 2 cm but less than 4 cm are called T2, greater than 4 cm are T3 and a tumor that deeply invades the

bone or tissues of the neck is labeled T4. Lymph node involvement is labeled as N1 if there is one lymph node less than 3 cm on the same side as the tumor. Lymph node involvement is labeled as N2 if a single lymph node is greater than 3 cm but less than 6 cm, or is on the opposite side of the tumor or if there is more than one lymph node enlarged. If a lymph node in the neck is greater than 6 cm then it is called N3. The M classification is M0 if there is no evidence of cancer spread elsewhere in the body or labeled as positive if there is evidence of cancer in distant tissues such as the lungs, liver, bones, or brain (AHNS, 2004). Once the TNM classification is completed the tumor is staged into one of four separate groups: I, II, III, or IV. Stages I and II are used for early stage tumors whereas stages III and IV are for advanced stage tumors. Overall survival rates for any cancer of the oral cavity are about 70% for 5-year survival with stage I and II disease. Five-year survival drops to about 50% for stage III cancers and to 35% for stage IV cancers (AHNS, 2004).

Treatment and Follow Up

Radiation therapy, chemotherapy, and surgery are commonly used, either alone or in combination, to achieve the best possible long-term outcome. Early stage cancers may be completely eradicated by surgery or radiation therapy alone. Advanced cancers usually require a combination of treatments and a prolonged course of recovery and rehabilitation (AHNS, 2004). Extensive invasion of oral cavity or neck tissues may require a muscle flap, usually from the chest wall, to restore function and preserve a more normal

appearance. There is a high rate of flap failure, oral cavity infections, fistula formation, and wound dehiscence (van Bokhorst de van der Schueren, van Leeuwen, Sauerwein, Kuik, Snow & Quak, 1997) The toxicity and complication profile of these multimodality therapies are among the highest of all oncology therapeutics. After a lengthy course of treatment the patient will be required to have frequent follow up visits to evaluate healing following 8 weeks or more of radiation and/or chemotherapy, as well as to ensure there are no signs of tumor re-growth. In general, about 70% of all the tumors that return do so within the first year after completion of treatment. Ninety percent of the tumors that return will appear within 18 months after treatment (AHNS, 2004). For patients that continue to smoke and drink alcohol following treatment there is a greater concern for the development of a second cancer.

Nutritional Alterations in Head and Neck Cancer

Patients who undergo major surgery for cancer often experience significant preoperative and postoperative immunosuppression that is multifactorial in origin. Malnutrition, surgical trauma, anesthesia, blood transfusions, and tumor burden all contribute to generalized depression of cellular and humoral immune function (Heys, Khan & Eremin, 1996). Patients with head and neck neoplasms present special nutritional and wound healing problems due to a history of smoking, dietary deficiencies, and heavy alcohol use. Pre- and post-surgical protein-calorie malnutrition results in impaired wound healing, reduced immunologic function, increased susceptibility to

infection, and decreased tolerance to effective cancer therapy. Complication rates are high with more than one study reporting an approximate 50% incidence of postoperative complications including wound breakdown and infection rates, averaging 21% and 30% respectively (Gianotti, Braga, Nespoli, Radaelli, Beneduce & diCarlo, 2002; Luis, Izaola, Aller, Cuellar & Terroba, 2005). Early clinical and experimental studies demonstrated that nutritional repletion before or during oncologic therapy restored immunologic function to normal and reduced operative morbidity and mortality (Mullen, Buzby, Matthews, Smale & Rosato, 1980). However, these early studies used parenteral nutrition support, were conducted in non-U.S. settings where differences in medical management might preclude generalization and, lacked measures of wound healing. A more recent study used enteral nutrition preoperatively for 7-10 days and achieved a 10% reduction in postoperative complications in patients with weight loss of 10% or more (Bertrand, Piquet, Bordier, Monnier & Roulet, 2002). There is now strong evidence suggesting that perioperative enteral nutrition supplemented with substrates such as arginine, glutamine, ribonucleic acids, and omega-3 fatty acids improves immune function and reduces postoperative complications (van Bokhurst-de van der Schueren, Quak, Flier, Kuik, Langendoen, Snow, et al., 2001). While still unclear as to the mechanism, it appears that enhancing the patient's immune status may attenuate the acute-phase response, decrease systemic

inflammation, and augment T cell function resulting in lowered susceptibility to postoperative infection (Barbosa & Wolfe, 2001).

The issues surrounding the care and treatment of patients with head and neck cancer extend far beyond the physiological insults and include severe psychological distress as well. Following surgery, patients will frequently have visible cosmetic deformities of the face and basic functional difficulties related to speaking, swallowing, eating, and mobility of upper extremities. The loss of taste and smell often results in alterations in dietary habits and diminished enjoyment of food that will impact nutritional status and quality of life long-term. Positive surgical outcomes along with individualized support for the life-altering changes following treatment may significantly influence future health and well being for patients with head and neck cancer.

Addressing the Problem

The discovery that perioperative immunonutrition appears to offer a benefit to head and neck cancer patients regarding late postoperative infectious complications means that more patients will have to supplement their diet with an immune-modulating formula at home prior to their surgical procedure. Today most patients undergoing elective surgical procedures even for malignant neoplasms only present to the hospital the day of surgery or perhaps the day before to complete the preoperative evaluation. Enlisting patient support for a preoperative nutrition intervention is necessary to accomplish the goal of priming the immune system for the impending insult of surgery.

Because this is not standard care it requires a focused research effort in the form of a pilot study to establish feasibility. Therefore, this pilot study was developed to examine the feasibility of a perioperative nutritional intervention in head and neck cancer patients for 7 days before and after surgery with measurement of selected nutritional, immunological, and wound healing outcomes.

Purpose

While controversy continues over the potential benefit and harm of immune-modulating formulas, national guidelines have been created for use of these formulas in selected populations of patients. These guidelines recommend using the formulas for surgical patients, especially those undergoing elective major surgery (Kudsk, Moore & Martindale, 2001). A summary of clinical trials reports that virtually all studies performed in patients undergoing elective surgical interventions demonstrated a significant reduction in infections of up to 50% when compared with controls (Sax, 1993, 2001; Suchner, Heyland & Peter, 2002). Also, laboratory data supported better recovery of postsurgical immune suppression when immunomodulatory formulas were used. The beneficial effect in surgical patients may be more prominent in malnourished patients but is also seen in well-nourished adults (Ochoa, Makarenkova & Bansal, 2004).

The high level evidence from clinical trials supporting immunonutrition in elective surgical patients was used as justification for the intervention in this study. In addition, several well-designed randomized clinical trials have specifically addressed immunonutrition support for patients undergoing surgery for cancer of the oral cavity and pharynx (Riso, Aluffi, Brugnani, Farinetti, Pia & D'Andrea, 2000; Snyderman, Kachman, Molseed, Wagner, D'Amico & Bumpous, 1999). The patients with head and neck neoplasms are excellent candidates for a research study that could potentially improve their surgical outcome. However, 61% of this patient population is diagnosed at a late stage (Ries et al., 2004) and surgery is scheduled urgently leaving limited time to intervene on nutritional status prior to surgery. The immunonutrition literature in the last 5-10 years has suggested that less time may be needed to achieve a beneficial effect in elective surgery patients than previously believed (Braga, Gianotti, Cestari, Vignali, Pellegatta, Dolci, et al., 1996; Braga, Gianotti, Radaelli, Vignali, Mari, Gentilini, et al., 1999). More recent studies of gastrointestinal cancer and head and neck cancer achieved success with reducing postoperative infectious complications with a narrow interval of intervention, 5-10 days before and after surgery (Ates, Yilmaz, Erkasap, Ihtiyar, Kaya, Pehlivan, et al., 2004; Luis, Izaola, Aller, Cuellar & Terroba, 2005). The many uncertainties related to timely access to the population, the selection of the immune-modulating formula, the length of time needed for the intervention to impact patient outcomes, and the selection of measurable

outcomes prompted this experimental pilot study. The purpose of the study was to establish the feasibility of providing perioperative nutrition support to head and neck cancer patients in one major military medical center.

Specific Aims

While the primary aim was to determine feasibility, three secondary research aims were developed so that findings from this study can contribute to the scientific literature regarding unreported short-term benefits of immunonutrition, such as improved wound healing. The specific aims of this research study were:

1. To determine the feasibility of providing perioperative nutritional supplementation, using either immune-modulating nutrition (IMN) support or standard nutrition support, to a convenience sample of adults at risk for nutritional deficits due to head and neck cancer (HNCA).

2. To compare the difference in the nutritional parameters, albumin and prealbumin, at specified time points, between adult patients at risk for nutritional deficits receiving IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

3. To compare the difference in immune response measured by cutaneous delayed-type hypersensitivity testing, lymphocyte counts, and lymphocyte subset counts between adult patients at risk for nutritional deficits

who received either IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

4. To compare the difference in surgical wound healing measured by visual inspection between adult patients at risk for nutritional deficits randomized to receive either IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

Significance

This study begins to address the current gaps in our understanding of the most appropriate utilization of immune-modulating nutrition. The study attempted to build upon the evidence we have for perioperative IMN and its impact on postoperative infectious complications. In addition, this study has included measurement of wound healing for the first time using a familiar and time-tested method, the ASEPSIS scoring method, to assess this short term outcome. Wound healing was selected as an outcome measure with the belief that it was more sensitive to the nutrition intervention and would ultimately be more useful than mortality as an outcome measure which is typically used in larger studies.

Even though the effects of surgery on the immune system are well described in many texts and journal articles, there are limited details about

surgery in the head and neck cancer patient who presents for surgery already immunocompromised. This study attempted to capture data that reflected the immune response to surgery in head and neck cancer patients with a variety of early and late stage tumors. The goal was to test the effect of nutritional supplementation, either with IMN or standard nutrition, on the post-surgical immune suppression looking for trends in immunologic parameters and the length of time required to return to baseline values.

Specialized nutrition support has evolved into a high priority therapy, backed by substantial scientific evidence. The next decade of immunonutrition research should focus on answering the lingering questions about the unique dietary components, the disease characteristics, and the dose required to achieve optimal patient outcomes. This pilot study was the first step in this process.

Chapter Two Theoretical Framework and Review of the Literature

Theoretical Framework

Introduction

The metabolic response to stress or surgery is a complex interaction of numerous mediators, including nervous system signals, hormones, and cytokine messengers. This network of physiologic responses is critical to the organism if it is to survive the insult. These responses are activated to liberate stored nutrients and substrates that will then support healing. The nutrients are utilized as oxidative fuels and contribute to the stabilization of organ function, maintenance of immuno-competency, and repair of injured tissue (Blackburn, 1988; Hensle & Askanazi, 1988). The importance of nutritional support for the metabolically stressed patient can not be overstated. Scientific inquiry has led to a better understanding of the molecular and biological effects of nutrients in maintaining homeostasis in the metabolically stressed population. However, nutritional intervention can be difficult in this population because of the alterations in nutrient utilization and limitations of nutrient delivery associated with critical illness.

The Biomedical Model of the Metabolic Response to Stress

Overview of the stress response.

The metabolic response to stress has been studied extensively ever since it was first described by Cuthbertson in relation to trauma, sepsis, and surgery (Cuthbertson, 1945). Many factors determine the extent of the

metabolic responses including the degree of insult, the persistence of the insult, the host response, the nutritional status of the host, and the timing in relation to previous insults (Martindale, Shikora, Nishikawa & Siepler, 2001). The metabolic responses can be divided into local responses and systemic responses. The local responses to insult or injury yield a predictable neurohormonal response that increases metabolic activity and increases local cellular work. The increases in energy consumption by the inflammatory cells and fibroblasts support collagen synthesis, matrix protein synthesis, and wound repair. The systemic response is characterized by an increase in the counter-regulatory hormones such as cortisol, epinephrine, and glucagon, as well as the stimulation of the cytokine cascade. The systemic response leads to altered protein synthesis, increased nitric oxide synthase, and an increase in leukocyte endothelial cell adhesion molecules (Fischer, 2001). In addition to the hormonal and cytokine response, other mediators augment the responses including reactive oxygen metabolites, nitric oxide, and arachidonic acid products (Hasselgren, 1999).

Cuthbertson's classical description of stress included two phases, an ebb phase and a flow phase. This description is still used today as the physiologic alterations continue to be the same. The ebb phase occurs immediately after the injury event and lasts approximately 24 to 48 hours. There is a noticeable increase in sympathetic activity and a stimulation of the hypothalamic-pituitary axis. This phase is characterized by significant

hypometabolism and decreased oxygen consumption. These findings are attributed to hypovolemia with a decrease in cardiac output and an inadequate oxygen transport to the tissues (Bessey, Downey & Monafo, 1992).

The second phase is the flow phase and it is characterized by hypermetabolism, catabolism, and increased oxygen consumption (Wilmore & Aulick, 1980). These mechanisms are mediated by hormones, cytokines, and nervous system signals from injured tissues. During this phase there is an active release of endogenous substrates such as glycogen-derived glucose, skeletal muscle-derived amino acids, and adipose tissue fatty acids (Blackburn, 1988; Cerra, 1987; Hensle & Askanazi, 1988; Rennie & Harrison, 1984). With limited glycogen stores and rapid depletion of glucose, the need for glucose will be met by enhanced muscle protein breakdown to provide amino acids for hepatic gluconeogenesis.

The net effect of these metabolic pathways is the provision of peripherally stored substrates to meet the energy and substrate requirements of the major organ systems. Each substrate plays a critical role in support of the stress response. Glucose is an important fuel for the central nervous system, the wound, and the immune system all of which are metabolically active during stress (Blackburn, 1988; Hensle & Askanazi, 1988; Wilmore & Aulick, 1980). Fatty acids are utilized for energy by the cardiac and skeletal muscle, the liver, and many other tissues. The majority of the amino acids are required for the synthesis of acute phase proteins, for thermogenesis, and as the

precursors for tissue repair (Blackburn, 1988; Hensle & Askanazi, 1988; Rennie & Harrison, 1984; Wilmore & Aulick, 1980).

Mediators of the stress response.

The stress response to illness or surgery is mediated by various hormones, protein messengers, and nervous system activity as mentioned previously. The counter-regulatory hormones include glucagon, catecholamines, and the glucocorticoids; all of which are found to be markedly elevated during surgical stress, trauma, sepsis or critical illness (Bessey & Low, 1993).The consequences of their elevation include increased protein mobilization, hyperglycemia, insulin resistance, and increased lipolysis. Glucagon stimulates gluconeogenesis, cortisol increases net protein catabolism, and the catecholamines result in glucose intolerance (Brillon, Zheng, Campbell & Matthews, 1995). The cytokines involved in this process are peptide messengers secreted by mononuclear cells or macrophages as a normal part of the inflammatory response during surgical stress and critical illness (Fong, Moldawer, Shires & Lowry, 1990; Starnes, Warren, Jeevanadam, Gabrilove, Larchian, Oettgen, et al., 1988). Cytokines act as hormonal regulators of the immune system. Important cytokines include tumor necrosis factor (TNF)/cachectin, interleukin-1 (IL-1), and interleukin-6 (IL-6). Correlations have been reported between the degree of up regulation of cytokine production and severity of illness and also the probability of death (Rixen, Siegel & Friedman, 1996). Cytokines also influence tissues such as the

gut mucosa, gut-associated lymphoid tissue (GALT), T cells, B cells, NK cells, the free and fixed macrophages of the liver, spleen, and the hepatocytes. The release of nitric oxide is critical for regulation of gastrointestinal motility, mucosal and splanchnic blood flow, and bile production.

Tumor necrosis factor induces a net catabolic state by mediating increased catabolism at the level of specific tissues, causing anorexia, and activating the hypothalamic-pituitary-adrenal axis (Starnes et al., 1988). The effects of TNF are dose-related and can potentially result in catastrophic tissue injury and fatal shock.

IL-6 is associated with the stimulation of the release of hepatic acute phase reactants to include C-reactive protein, fibronectin, antitrypsin, ceruloplasmin, and 1-acid glycoprotein. Albumin is a negative acute-phase protein, and its synthesis is curtailed by inflammation. The release of acute phase reactants is part of the systemic inflammatory response syndrome (SIRS) which is a normal host response to an inflammatory process such as surgery, infection, or trauma. This response is characterized by generalized activation of the vascular endothelium and polymorphonuclear cells. Again, the net result is the mobilization of endogenous substrates for tissue repair, energy, and support of the immune system (Martindale, Shikora, Nishikawa & Siepler, 2001).

Immunologic response.

As part of the well-coordinated response to infection and injury, the inflammatory mediators discussed above release substrate from their host tissues to support B and T lymphocyte activity thereby creating a hostile environment for pathogens. These inflammatory mediators raise body temperature and produce oxidant substrates that initiate downregulation of the process once invasion has been defeated. The majority of patients survive the systemic inflammatory response syndrome (SIRS) and after a period of relative clinical stability, manifest a compensatory anti-inflammatory response syndrome (CARS) with suppressed immunity and diminished resistance to infection. The interaction between the innate and adaptive immune system seems to be an important inductor of both SIRS and CARS. It appears that T cells from the adaptive immune system play a role in the early SIRS response to injury and to CARS (Correia & Almeida, 2005).

The alteration in nutrient homeostasis that accompanies metabolic stress has presumably evolved to enhance the chances for survival. However, the patient with head and neck cancer experiences a prolonged state of metabolic stress that places them at very high risk for nutritional and immunological deficits that only serve to threaten survival. Cancer cachexia, extended periods of low appetite, nausea, swallowing difficulties, and pain all contribute to the unique nutritional challenges facing the patient with head and neck cancer.

Nutritional Alterations in Cancer

The diagnosis of cancer has traditionally been associated with malnutrition and wasting. The deterioration of overall nutrition status is termed cachexia; it is estimated that half of all oncology patients experience cachexia (Finley, 2000). The cancer cachexia syndrome involves widely variable physiologic and metabolic derangements resulting in potentially life-threatening malnutrition. Nutritional alterations may stem from the tumor, treatment effects, or the patient's reaction to the diagnosis. The tumor may induce cachexia through mechanical obstruction of the gastrointestinal tract, release of cytokines, or increase in metabolic rate. Surgery of the head and neck often results in difficulty swallowing (Finley, 2000; van Bokhurst-de van der Schueren et al., 1999). Chemotherapy and radiation therapy contribute to cachexia through a variety of side effects such as anorexia, nausea and vomiting, diarrhea, mucositis, thickened secretions, and taste alterations (Minasian & Dwyer, 1998). A cancer diagnosis may lead to depression, anxiety, anger, and fear, which can also affect appetite and the motivation for oral intake. All of these factors can result in severe weight loss, which potentially affects prognosis, ability to heal, length of recovery, and cost of care.

Tumor and host tissues produce a variety of cytokines that appear to induce abnormal carbohydrate, protein, and fat metabolism, and anorexia. Tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), and

interferon-γ are the implicated cytokines. TNF and interferon-γ have been shown to inhibit the enzyme lipoprotein lipase, leading to increased fat mobilization. Interleukin-1, IL-6, and TNF are implicated in accelerated protein metabolism and muscle wasting (Tisdale, 1998). Many cytokines induce the synthesis of other cytokines in a cascade effect, making it difficult to differentiate which cytokine is responsible for the cachectic effect (Moldawer & Copeland, 1997).

Perioperative Nutritional Support in Head and Neck Cancer

Patients with head and neck cancer are at particular risk for malnutrition before, during, and after their surgical treatment. Alcoholism, tobacco use, and poor diet are prevalent in this population and lead to altered intake and metabolism of protein, vitamins, and minerals. In addition, reviews suggest that the continuous exposure of immunocompetent cells to alcohol suppresses the immune system (NIAAA, 1993). Allowing a patient's nutritional state to deteriorate through the perioperative period adversely affects measurable outcomes related to nosocomial infection, multiple organ dysfunction, wound healing, and functional recovery. A lack of nutrition has several immediate pathophysiological consequences including inhibition of saliva and digestive tract secretions, reduced gastrointestinal (GI) motility and splanchnic circulation, absence of stimulatory nutrients such as short chain fatty acids which can upset the normal GI flora, atrophy of the mucosa of the small intestine and colon, and impaired gut-associated lymphoid tissue

(GALT) function. This results in impaired nutrient absorption and reduced GI integrity (O'Flaherty & Bouchier-Hayes, 1999).

The potential importance of preoperative supplementation was shown by Flynn and Leightty (1987) who studied 36 patients who were considered malnourished before surgical treatment of their head and neck malignancies (Flynn & Leightty, 1987). Nineteen patients were randomized to receive enteral nutritional supplementation before surgery, whereas 17 patients were randomized to receive only nutritional counseling and no supplementation. Despite a bias toward a worse prognosis in the supplemented group, fewer complications occurred in this group, and there was a reduction in both postoperative morbidity and length of hospital stay compared with the unsupplemented group. Several studies in patients with gastrointestinal malignancies conducted by a team of Italian investigators demonstrated that patients receiving preoperative enteral nutrition had 20% to 60% fewer major postoperative complications when compared with a control group receiving standard oral diet (Braga et al., 1996; Braga et al., 1999; Senkal, Kemen, Homann, Eickhoff, Baier & Zumtobel, 1995).

While the majority of early clinical trials in head and neck cancer patients focused on postoperative enteral support, today the emphasis is on perioperative hypotheses. Researchers and clinicians alike recognized that if the peak inflammatory response occurred approximately 3-5 days after surgery, then any nutritional intervention designed to downregulate or suppress

this response must be administered prior to surgery in order for it to achieve its optimal effect several days later. Furthermore, the data supporting early postoperative enteral feeding is convincing enough that any patient in need of artificial nutrition following surgery should begin enteral feedings within 24-48 hours (A.S.P.E.N., 2002).

There are few patients as nutritionally compromised as the head and neck cancer patient presenting for curative surgery. While most patients will follow surgery with a rigorous regimen of chemotherapy and/or radiation therapy, some will undergo tumor-debulking radiation prior to surgery. Despite data showing 35-50% of head and neck cancer patients are malnourished preoperatively it is uncommon to find a patient with an artificial feeding device in place prior to surgery or a nutritional repletion regimen including supplements prescribed by a registered dietitian. In fact, preoperative oral or enteral nutrition support is not yet standard of care.

Immunonutrition

One frequently cited definition of immune-modulating nutrition (IMN) is, modulation of the activities of the immune system by nutrients fed in amounts above those normally encountered in the diet and the consequences to the patient of immune activation (Grimble, 2001). The literature defines immune-enhancing nutrition the same way and the terms may be used interchangeably. Important targets for immunomodulation are: enhancing the cell-mediated response, altering the balance of pro- and anti-inflammatory

cytokines, prevention of excessive activation of nuclear factor κ-B, facilitation of optimal activity of activator protein-1 and moderation of tissue nutrient depletion (Grimble, 2001). The mechanisms of host protection are mediated by the ability of immunonutrients to support immune defense mechanisms, inflammatory response, intestinal barrier function, tissue oxygenation, and ischemia/reperfusion injury. The inflammatory response to injury and infection, although an essential part of immune function, carries the risk of severe tissue depletion and immune suppression (Refer to Figure 1.). These outcomes increase morbidity and delay recovery (Grimble, 1996). Within minutes of the surgical trauma an ischemia/reperfusion injury is initiated and inflammatory and microvascular changes take place. The resulting proinflammatory cytokine cascade leads to three key processes which influence patient outcomes. These processes are 1) creation of a hostile environment (for pathogens), 2) provision of nutrients for the immune system from endogenous sources, and 3) strengthening of the protective and control systems against damage to healthy tissue by the immune response. Inhibitory systems come into play with the objective of terminating the response once its primary purpose of defeating pathogens has been achieved. There are a number of undesirable consequences if the immune system is overactivated to include: 1) immunosuppression and hyperinflammation, 2) oxidant damage, and 3) excessive loss of tissue components (Grimble, 2001). Major surgery may have a profound effect on the number of total T-cells, suppressor or cytotoxic T-

cells and natural killer cells, which are all reduced at postoperative day 3 (O'Flaherty & Bouchier-Hayes, 1999). These impairments are usually transient and it is imperative that normal function is restored quickly in order to facilitate wound healing and to combat infection.

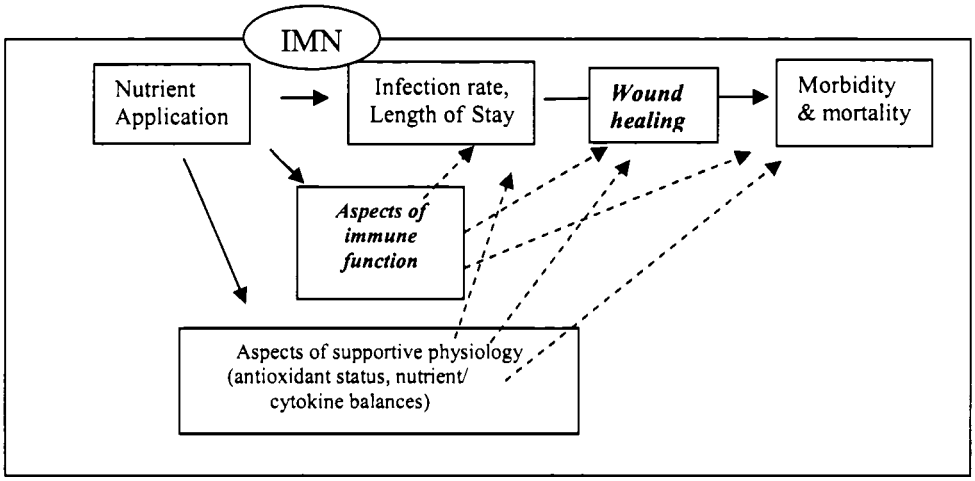

Figure 1 Key areas influenced by IEN (adapted from Grimble, 2001)

The dietary compounds that have been added to standard enteral formulations have been shown to have several unique characteristics (Table 1). Among those most carefully investigated is arginine, which improves immune cell activity and vasodilatation through the production of nitric oxide (Reynolds, Daly & Zhang, 1988); ω-3 polyunsaturated fatty acids (PUFA) derived from fish oil, which are potent anti-inflammatory agents through the modulation of eicosanoid synthesis and upregulate the immune response (Kinsella, Lokesh, Broughton & Whelan, 1990) and glutamine which is known to reduce skeletal and intestinal protein waste during stress, to enhance the macrophage and neutrophil phagocytosis, and preserve the intestinal permeability (Hall, Heel & McCauley, 1996). The administration of diets

enriched with ω-3 PUFA has shown reduced plasma and tissue levels of specific leukotrienes, thromboxanes, and prostaglandins which exert proinflammatory and immunosuppressive effects (Daly, Weintraub, Shou, Rosato & Lucia, 1995; Kenler, Swails & Driscoll, 1996). Presently, it is not clear whether it is the combination of immunonutrients that is crucial, rather than any one nutrient in particular. Based on studies reported in the literature combination immunonutrition seems to be more powerful (Barton, 1997).

Table 1. Common immune-enhancing nutrition components and their function

Nutrient	Physiologic function	Effect on immune response/infectious complications/wound healing
Omega-3 PUFA	Found abundantly in fish oil. Main function is structure and function of cell membranes & regulation of cell metabolism	Improves immune function and reduces acute and chronic inflammation. Alters cytokine production and release from macrophages. Provides resistance to infection while inhibiting inflammation and platelet aggregation. Substitution of arachidonic acid by eicosapentanoic acid results in a milieu that is immune enhancing and anti-inflammatory (Heyland, Cook & Guyatt, 1994)
Nucleotides	Building blocks for DNA & RNA, involved in all cell activities; transfer of energy, coordination of hormonal signals, & protein synthesis.	Lymphocytes require more nucleotides to mount an effective immune defense. Individuals are more susceptible to infection without dietary nucleotides. Nucleotides are integral to cell mediated immunity and T-lymphocyte function and maturation; an increased amount should be provided in the diet during stress/illness (Heyland et al. 1994)
Glutamine	Conditionally essential amino acid; represents 60% free amino acids in muscle and 20% in plasma. Acts as an oxidative fuel for rapidly dividing cells such as GI mucosal cells and immune cells. Essential for normal cell proliferation and tissue growth.	Glutamine supplementation before surgery for colorectal cancer had a significant increase in T cell lymphocyte DNA synthesis compared to patients receiving no glutamine. It serves a role in wound healing by acting as a fuel to fibroblasts and stimulated lymphocytes (Meyer, Muller & Herndon, 1994).
Arginine	Conditionally essential amino acid; during times of stress & growth, endogenous synthesis is insufficient to meet body demands (Schloerb, 2001). Is a substrate for protein, creatinine and polyamine synthesis. Is a precursor for proline & hydroxyproline and thus collagen synthesis (Barbul, 1983).	Improves nitrogen balance after injury, enhances wound healing, and affects T lymphocyte functional parameters in animal and human studies (Barbul, 1990). Supplementation with arginine following major surgery or trauma has resulted in a faster return of normal T-cell function after day 7 of feeding (Reynolds, Daly & Zhang, 1988).

Wyncoll and Beale (2001) summarized the results of a meta-analysis of immunonutrition trials (both perioperative and postoperative) by stating that a substantial body of consistent evidence incorporating more than 2,500 patients, most of whom underwent major surgery for cancer or experienced severe trauma, strongly suggests that immunonutrition is not harmful and is very likely beneficial. They continue to say that there is clearly considerable scope for more research with some of the newer formulations, particularly regarding the issues of dose, timing, duration of administration, and the value of particular substrates in specific patient groups (Wyncoll & Beale, 2001).

Effect of IEN on Immune Function

Changes in both cell-mediated and humoral immunity are responsible for the increase in infectious complications in critically ill patients. In general, critically ill patients suffer from defects in skin recall responses, B and T-cell function, and polymorphonuclear leukocyte chemotaxis (Simms, 1999). The focus of research in this field has evolved from strictly postoperative nutrition support to perioperative nutrition support, with one study now suggesting that preoperative nutrition support alone may provide the same protective benefits in terms of immune function and infectious complications (Tepaske et al., 2001). It seems unrealistic to expect patients who have undergone major surgery to begin the healing process without any postoperative nutrition support. The argument is being made by Tepaske et al. (2001) because so many feeding issues arise following major surgery that the patient may go

several days without adequate nutrition. If the patient has received the immune-modulating nutrition preoperatively there may be a protective benefit before nutritional deficits become substantial and harmful.

Postoperative.

A meta-analysis of twelve randomized controlled trials containing over 1400 surgical patients receiving postoperative IEN with the key nutrients arginine, ω-3 fatty acids, RNA-nucleotides, and glutamine concluded that IEN is superior to standard nutrition in terms of infection rate and hospital length of stay for patients with critical illness, even on an intent-to-treat basis (Beale, Bryg & Bihari, 1999). Daly and coworkers (1995) found that postoperative IEN resulted in fewer infectious and wound complications ($p<0.05$) and a shorter hospital stay ($p<0.01$). The decrease in length of stay reported by Daly's group was found only in the subgroup of patients who completed the study. Other studies carried out in surgical patients have demonstrated that early postoperative administration of IEN resulted in a better immune response after surgery compared to standard diets. In particular, a significant augmentation of delayed hypersensitivity response, macrophage phagocytosis ability, lymphocyte blastogenesis, CD3+ and CD4+ subset proliferation, as well as reductions in cytokine levels (Senkal et al., 1995; Daly et al., 1995; Braga et al., 1996).

Perioperative.

Experimental studies have been conducted that strongly support the usefulness of IEN given before and after injury in preventing late infectious complications (Snyderman et al., 1999). The majority of studies investigating the immune benefits of IEN in reducing surgical complications involve patients undergoing resection of gastrointestinal cancer (Braga, Gianotti, Vignali & DiCarlo, 1998; Daly et al.,1995; Senkal et al., 1999), with fewer studies conducted in head and neck cancer patients (Riso et al., 2000; Snyderman et al., 1999). Significantly improved outcome associated with the use of IEN has been reported in both populations. Perioperative feeding of colorectal cancer patients with an arginine-enriched enteral feed containing ω-3 fatty acids resulted in a decrease in the postoperative rise in IL-6 and IL-1 soluble receptors, an improvement in delayed hypersensitivity responses, and a decrease in infection rates (Gianotti et al., 1999). Other studies (Senkal et al., 1995; Snyderman et al., 1999) involving surgical patients supplemented with perioperative IEN had similar results of decreased infectious complications, total hospital stay, or postoperative length of stay when compared to patients receiving standard nutrition formulas. A series of investigations by Braga and associates (Braga et al., 1999; Braga et al., 1998; Braga et al., 1996) failed to show a significant effect on LOS or frequency of infectious complications, although the perioperative IEN significantly improved postsurgical immunosuppression and inflammatory responses, and gut function in patients

with GI cancer. Using a perioperative nutrition design, a group of investigators demonstrated that preoperative immunonutrition is superior to standard supplement and is able to offset the early postoperative immune depression in patients undergoing major abdominal surgery, as shown by significantly increased T lymphocytes and immunoglobulin class M levels (Senkal et al., 1995).

Preoperative.

A more recent study by Tepaske et al. (2001) was designed to test the hypothesis that a preoperative oral immune-enhancing nutritional supplement could improve preoperative host defense, and subsequently lower postoperative infections and organ dysfunction in elective cardiac surgery patients over the age of 70. They found preoperative expression of HLA-DR epitopes on monocytes was significantly higher in patients given the study treatment and delayed-type hypersensitivity response to recall antigens was improved preoperatively and remained better until discharge. Gianotti et al. (2002) reported their findings from 305 patients undergoing surgery for gastrointestinal cancer randomized to one of three groups: 1) oral supplementation with 1L/day of IEN for 5 days before surgery, 2) same preoperative treatment plus postoperative jejunal infusion with IEN, and 3) no artificial nutrition before or after surgery. Intention–to-treat analyses showed a 13.7% incidence in postoperative infections in group 1, 15.8% in group 2, and 30.4% in the conventional group ($p=0.006$ vs preoperative; $p=0.02$ vs

perioperative). The researchers concluded that preoperative supplementation is as effective as perioperative administration in improving outcome and both strategies seem superior to the conventional approach. While the suggestion that preoperative IEN support alone may offer enough protection from postoperative complications, it is unlikely that nutrition support would not be provided to a critically ill postoperative patient.

Conclusion.

A review of noteworthy studies thus far (Senkal et al., 1995; Tepaske et al., 2001; van Bokhurst-de van der Schueren et al., 2001; Braga et al., 1999; Gianotti et al., 2002) indicates that the use of nutrients in pharmacologic doses to enhance immunity is not only safe but also effective. Whether IMN formulas are beneficial, or whether they are beneficial only in selected patient populations remains controversial. Increasingly, doctors are finding antibiotics are not a universally satisfactory solution to infections in critical care patients due to the emergence of highly resistant organisms (Novartis, 2003). Evidence in recent years suggests that IEN can help tip the balance in favor of selected patients by enhancing immune function, however we lack studies in the most vulnerable groups, for example HNCA patients. Immunonutrition can ameliorate the catabolic and immunological response to major surgery but is most effective in reducing postoperative infectious complications when administered for a minimum of 5 days in the preoperative period (Senkal et al., 1999).

This pilot study was designed to incorporate all of the latest findings into a perioperative intervention for HNCA patients at high risk for postoperative infectious complications and impaired wound healing. The 7-day pre- and post-operative supplementation with either IMN or standard nutrition, the prescribed amount of 960-1200 mL of supplement, and the measurement of nutritional and immunologic parameters was developed to further the science of timing and dose, as well as impact on biologic markers of inflammation and infection.

Chapter Three Methods

Design

A randomized, experimental, two group design with 12 subjects was used to pilot test this intervention and provide evaluation of the intervention's feasibility and potential impact on cellular and surgical outcomes (Alvarez & Mobarhan, 2003). The design included a treatment group and a control group or a "relative comparison" group that received a standard or typical treatment as opposed to receiving no treatment. The investigator felt including a group that did not receive a nutritional intervention was contrary to what is currently published about perioperative nutrition support. In addition, it is not medically beneficial nor is it ethically acceptable to withhold feedings for 7 days postoperatively for any surgical patient today (Braga et al., 2002). Standard or typical treatment for head and neck cancer patients is that they are often told to increase their caloric intake prior to surgery by consuming over-the-counter supplements such as Ensure® or Boost®.

A review of immunonutrition studies designed to provide only preoperative nutrition support (before surgery), only postoperative nutrition support (after surgery), or perioperative nutrition support ("around" or before and after surgery) strongly suggests that perioperative support provides the greatest benefit in terms of reduced infectious complications and shorter hospital stay (Senkal et al., 1999). This is the reason perioperative nutrition support was chosen for this pilot study.

The study was double-blinded, keeping the PI and the patient's surgical team, as well as the patient, unaware of the group assignment. A research assistant (RA) assigned to the team was hired so that the formula could be delivered to the patient while keeping the PI blinded. It was also the RA who phoned the patients each day to check in with them and answer any questions they had regarding the formula or the protocol. No attempt was made to mask the label on the products but patients were simply told they had a 50:50 chance of being in the immunonutrition group versus the standard nutrition group during counseling. They were not explicitly told which group they randomized to when the formula was delivered. The surgical residents wrote the postoperative orders for the patients and therefore had knowledge of the group assignment but the surgeon who performed the actual surgery, monitored the patient's postoperative course, and rated wound healing, did not know the group assignment.

Sample

Sample recruitment and selection.

Study participants were 12 volunteers with a diagnosis of head and neck cancer who met study inclusion criteria (see Table 2). Participants were recruited over a 16-month period from the Otolaryngology, Head and Neck Service at Madigan Army Medical Center. This 172-bed tertiary care military medical facility in Tacoma, Washington serves as a referral center for the areas of Alaska, Hawaii, and the South Pacific as well as Oregon, Washington,

Idaho, and Montana. Head and neck cancer cases are military beneficiaries presenting for care or Veterans Administration (VA) beneficiaries routinely referred from the nearby American Lake Veterans Administration Hospital. The Otolaryngology, Head and Neck Service schedules 1-2 patients each month for radical neck dissection, modified radical neck dissection, or other curative surgery for head and neck neoplasms. Volunteers were solicited who were experiencing their first head and neck cancer diagnosis or who experienced a previous HNCA diagnosis greater than 6 months prior to initial contact with study personnel. Due to the limited number of potential candidates and the fact that all candidates were referred to the same clinic, no aggressive marketing or recruiting techniques were required.

Table 2. Study Inclusion Criteria

Active duty and retired military service members and their dependents or VA beneficiaries
Adults greater than 18 years of age
Ability to speak and understand English
Signed and witnessed consent form
Non-pregnant females
Permission of attending physician
Diagnosis of head or neck cancer (except thyroid gland) with surgery scheduled $\geq$ 8 days from initial contact
Evidence of nutritional deficits; albumin $\leq$ 3.5gm/dL or weight loss $\geq$ 10% in previous 6 mos
No contraindication to consumption of either study formula; e.g. no allergy to milk or fish oil
Reside in the greater Puget Sound area of Western Washington (range ~100 miles from hospital)

A cancer of the head and neck was defined as a cancer of the oral cavity, pharynx, paranasal sinuses, larynx, or salivary glands. Tumors of the salivary glands behave differently and display histologic features different from the other sites. The head and neck cancer literature includes tumors of the thyroid gland; however, patients with these tumors were excluded from this

sample population. Table 3 lists subsites of tumor locations. These sites are noteworthy for their relationship to normal swallowing and eating.

Table 3. Subsites of HNCA tumor location

Primary Location	Subsites
Oral cavity	Lips Buccal mucosa Floor of mouth Oral tongue Hard palate Gingivae
Pharynx: Oropharynx	Faucial arch Tonsilar fossa, tonsil Base of tongue Pharyngeal wall
Pharynx: Nasopharynx	Posterosuperior wall Lateral wall
Pharynx: Hypopharynx	Pyriform fossa Postcricoid area Posterior wall
Larynx	Supraglottis Ventricular bands Arytenoids Suprahyoid epiglottis Infrahyoid epiglottis Glottis Subglottis

American Joint Committee on Cancer® CancerStaging Manual (5th Edition), 1997. Philadelphia: Lippincott-Raven.

Many patients only presented for their initial evaluation once swallowing or eating became difficult or painful. Often times this meant that the patient had altered their diet to consist primarily of liquids or soft foods and subsequently experienced minimal to severe weight loss as a result.

Sample size.

The sample size of 12 patients was based on the projected number of participants who could enroll and complete the study over a one year period. There are no formal recommendations for sample size in a pilot study. The

sample size was large enough to potentially detect trends in the data but not so large that it would require a lengthy period of time for data collection and create an unnecessary burden on patients for follow-up.

Experimental or treatment group.

The experimental group received Impact Recover® (oral drink) or Impact Glutamine® (tube feeding) (Novartis Nutrition, Bern, Switzerland) preoperatively. Impact Recover®, an immune-modulating beverage, was developed by the company so that patients could drink it as a supplement if they did not have an artificial feeding device. It was not designed to be a complete diet that would be infused via feeding tube continuously. Patients in the experimental group received Impact Glutamine® postoperatively if they had a feeding device. Both products are commercially available nutritional supplements containing high protein, arginine, glutamine, ribonucleic acids, and omega-3 fatty acids. Having both an oral drink and a tube feeding formula allowed for recruitment from the largest possible group of eligible patients. For this study patients were asked to consume a minimum of 4 servings each day of Impact Glutamine® and 5 servings each day of Impact Recover® in order to meet the consensus recommendations of providing 50% to 60% of the patient's calculated daily needs (A.S.P.E.N., 2001; McClave, Snider & Spain, 1999). There are also studies that advocate a minimum of 1000 mL of preoperative immune-modulating nutrition per day in order to see the benefits in postsurgical outcomes. The protocol provided 960-1200 mL per day, 1200-

1440 kcal/day, and a significant dietary intake of key vitamins and minerals. Caloric distribution for Impact Recover® of 29% protein, 46% carbohydrate, and 25% fat and a caloric density of 1.0 cal/mL has been shown to meet the metabolic needs of high risk and acute or critically ill medical and surgical patients. Impact Glutamine® provided the same immune-modulating components, 24% protein, 46% carbohydrate, and 30% fat, and a caloric density of 1.3 cal/mL. Arginine and glutamine account for the higher amounts of protein in both formulas. Impact Glutamine® was selected from several immune-modulating formulas because it is the product most similar to Impact Recover® (See Table 4. Product Description). Experimental group patients were instructed to consume the supplements for 7 days before surgery. For most patients in this group a complete tube feeding diet was ordered for a minimum of 7 days after surgery.

Control group or relative comparison group.

The control group received Isosource 1.5® both preoperatively and postoperatively. It is a high calorie, high nitrogen, complete liquid diet that comes vanilla-flavored for palatability. It is sold in the familiar 8 ounce cartons that look like a juice box. Control group patients were asked to consume 4 servings (~1440 calories) per day for 7 days as a supplement or tube feeding preoperatively. They received full nutritional support based on energy requirements for a minimum of 7 days postoperatively. Caloric distribution of

18% protein, 44% carbohydrate, and 38% fat, and a caloric density of 1.5 cal/mL meets the needs of patients who are mildly or moderately malnourished or acutely ill (Novartis, 2003).

Table 4. Product Description (amts are per 8 oz serving)

Components	IMPACT Recover (oral)	IMPACT Glutamine	Isosource 1.5
Calories	240 (1.0/mL)	325 (1.3/mL)	360 (1.5/mL)
Protein g	17	19.5	16.9
Carbohydrate g	26	37.4	42
Fat g	6.6	10.8	16.2
Arginine g	4.1	16.3	-
Dietary Nucleotides g	3.9	1.6	-
Omega-3 fatty acids g	4.2	2.7	-
Glutamine g	12	15	-
Recommended intake	5 packets/day	4 servings/day	4 servings/day
Total mL/day	1200 mL/day	960 mL/day	960 mL/day
Total calories/day	1200 kcal/day	1408 kcal/day	1440 kcal/day

Human Subjects

This study received approval for research with human subjects from the Institutional Review Board (IRB) for the University of Washington Human Subjects Division, the Madigan Army Medical Center and the Army Medical Command's Clinical Investigations Regulatory Office (CIRO), as well as the IRB for the Uniformed Services University of Health Sciences which provides oversight for protocols funded by the TriService Nursing Research Program. Volunteers underwent informed consent procedures and signed a written consent form prior to study participation (See Appendix A, Consent Form).

Setting.

Study enrollment took place in a private treatment room in the Ear, Nose, and Throat Clinic at Madigan Army Medical Center. Following consultation with the surgeon from the Otolaryngology, Head and Neck Service, one of the clinic Residents would notify the investigator of a potential candidate for the study. The investigator met with the patient and any family members present to discuss the protocol in detail, answer their questions, and obtain informed consent. Because surgical treatment was expedited for these patients many were enrolled only 8-10 days before surgery. The preoperative nutrition intervention took place in the home for 7 days before surgery; studies report benefit from 5 – 10 days (Braga et al., 1999). The postoperative intervention was also planned for 7 days based on the literature and the historical average length of stay in this hospital for surgical HNCA patients. The typical hospital course following radical neck dissection or modified neck dissection is a 1-2 day stay in the Intensive Care Unit followed by 5-7 days on the surgical floor. The nursing staff was familiar with the care of these patients which often included tracheostomy care, airway management, pulmonary toilet, tube feedings, and wound care.

Data Collection

Timeline.

Data collection occurred from August 2004 through December 2005. Participant enrollment was steady but slow throughout this period of time. It was anticipated that subject recruitment would take about 12 months but due to

fewer patient referrals during this time, the study period was extended. Therefore the total data collection period was 16 months.

Procedure, preoperative period.

Study procedures for each patient are summarized in Table 5. As volunteers were recruited, permission for participation from their head and neck surgeon was obtained, and the investigator discussed all details of the protocol. Once informed consent was obtained, appointments were made for baseline consultations. These included nutrition care, speech pathology, and immunization clinic. These consultations were conducted before surgery but occasionally were arranged by the patient from home. On the day that the patient consented to participate in the protocol demographic information was recorded for age, gender, height, weight, diagnosis, risk factors, tumor category, and prior radiation therapy (See Appendix B, Demographic Form). Prior to leaving the ENT Clinic all patients had an appointment scheduled for the Surgical Services Center which included preoperative surgical consultation with anesthesia and nursing staff, as well as referrals for electrocardiograms, radiographic films, and laboratory tests as needed. Laboratory tests performed upon enrollment into the study were labeled as baseline values and included complete blood count, lymphocyte subsets (CD3, CD4, CD8, CD4:8, CD19, and CD56), albumin, prealbumin, and C-reactive protein. The immunization clinic performed a delayed-type hypersensitivity (DTH) skin test at baseline as well. This skin test was read 48-72 hours later either by the RA at the patient's

home or by the Immunization Clinic staff if the patient was willing to return to the hospital. If the patient received a percutaneous endoscopic gastrostomy (PEG) tube prior to surgery he/she also saw the Oncology Clinical Nurse Specialist for education about the use and care of the feeding tube prior to discharge. Every effort was made to cluster appointments for the patient to minimize the number of trips back and forth to the hospital. It was also important to accomplish the preoperative workup while still allowing the patient an opportunity to follow the nutrition supplementation protocol for 7 full days. A preoperative PEG tube placement required up to 32 hours of nothing by mouth; 8 hours before the procedure and 24 - 48 hours after the procedure.

The majority of patients were able to tolerate some additional oral intake although for many it was liquids and soft foods providing far less energy intake than their estimated energy requirements. The dietitian performed the initial nutritional consultation and made recommendations for oral intake along with the nutritional supplement the patient received as part of the study protocol. During the visit with the dietitian the patient completed the Patient-Generated Subjective Global Assessment tool (See Appendix C, PG-SGA tool). Part one of this tool requests input from the patient so that they can provide any history regarding changes in their diet, their appetite, their weight, their symptoms, or their activities. Part two is completed by the dietitian following a thorough history and assessment. The tool is then scored to

provide an evaluation of nutritional risk, classifying patients as having a minimal, moderate, or severe risk.

On the day of enrollment the research assistant (RA) was notified of the new study patient. Her role was to select the appropriate numbered envelope, open it to reveal the randomized group assignment, and make arrangements to deliver the supplement to the patient's home. The formula was delivered to the patient's home in time for the patient to receive 7 days of preoperative supplementation.

Patients were asked to maintain a diary of meals, snacks, and beverages consumed during the 7 days before surgery (See Appendix D, Subject Diary). This diary was used to record other dietary intake, reasons for not following the feeding protocol, gastrointestinal symptoms, and concerns or questions for the RA. Diary entries were discussed with the RA during the daily phone call. Each day for the 7 days of preoperative feeding the RA phoned the subject to ask about adherence to the feeding protocol, questions regarding artificial feeding devices, or general concerns about their diagnosis, their upcoming surgery, or the research study. Subjects were reminded to save all formula containers and to bring them to the hospital the day of surgery, along with the diary.

Procedure, postoperative period.

The postoperative protocol was devised based on the typical hospital course of 7-10 days. Postoperative support was provided in the hospital setting unless the patient was discharged early and then he or she completed the remaining formula at home. Within 24 hours following surgery, both groups were scheduled to start their respective nutritional support by nasoenteric feeding tube or PEG tube for 7 days. The investigator or a Research Associate ensured feedings were restarted as planned. Because the patient had no other nutritional intake, the dietitian made recommendations for full caloric support and feedings were initiated per institutional protocol. While hospitalized, data regarding nutritional intake (volume of feeding prescribed/received, % caloric goal achieved) and gastrointestinal symptoms were recorded daily. Protocol biochemical laboratory tests were again drawn on the day of surgery (DOS), postoperative day 1 (POD 1), POD 4, and POD 8; these included complete blood count, lymphocyte subsets (CD3, CD4, CD8, CD4:8, CD19, and CD56), albumin, prealbumin, and C-reactive protein. Nosocomial infections and/or wound complications were recorded as they occurred. Wound assessments using the ASEPSIS scoring method were performed daily and photographic images were taken on POD 1, 4, and 8. A repeat DTH skin test was scheduled for POD 8. Postoperative follow-up visits were scheduled by the Surgeon or Chief Resident upon discharge, usually for once a week on Wednesday. During this visit wounds were evaluated, swallowing and speech were assessed, and pain or other symptoms were addressed as needed. Barium swallows were

often performed the first week postoperatively to determine if it was safe for the patient to start an oral diet. These visits provided an opportunity for research team members to meet with the patient and assist with any medical or psychosocial issues that had developed since discharge. On POD 15, 22, and 29, a wound healing assessment was performed by the physician and nurse jointly. On POD 29 the subject completed the interventional study period and the investigator recorded data regarding hospital outcome, wound healing outcome, and infectious complications.

Table 5. Procedures

<table>
<tr><td></td><td>Base-line</td><td>Study Day 1</td><td>Study Day 7</td><td rowspan="11">SURGERY</td><td>Study Day 9 POD1</td><td>Study Day 13 POD4</td><td>Study Day 17 POD8</td><td>Study Day 24 POD15</td><td>Study Day 31 POD22</td><td>Study Day 38 POD 29</td></tr>
<tr><td rowspan="3">Routine procedures</td><td>Labs: alb, prealb, CBC</td><td></td><td>NPO after MN</td><td>Labs</td><td>Labs</td><td></td><td>ENT F/U visit</td><td>ENT F/U visit</td><td>ENT F/U visit</td></tr>
<tr><td></td><td></td><td></td><td>RD Con-sult</td><td>RD Con-sult</td><td colspan="2">Anticipate discharge during this time period</td><td colspan="2">RD Consult prn</td></tr>
<tr><td>Speech consult</td><td></td><td></td><td colspan="5">Speech consult prn</td></tr>
<tr><td>Nutrition Support Protocol</td><td>RD Consult</td><td>Both groups start NS</td><td>Con-sume NS before MN</td><td>Restart NS, same formulas</td><td>NS</td><td>Change to std formula or po intake</td><td colspan="3">Continue feedings as recommended by RD</td></tr>
<tr><td rowspan="3">Study procedures</td><td rowspan="2">Lymph Subsets CRP, DTH</td><td colspan="2"></td><td colspan="3">Begin wound monitoring (ASEPSIS score/wound photo) until d/c</td><td colspan="3">ASEPSIS score @ clinic visit; wound photo prn</td></tr>
<tr><td colspan="2">Begin daily phone calls until Surgery</td><td rowspan="2">Labs</td><td></td><td></td><td>Final labs; DTH</td><td colspan="3">Document # infections, LOS</td></tr>
<tr><td>SGA</td><td colspan="2">Home visits prn</td><td colspan="3"></td><td colspan="3"></td></tr>
<tr><td>Out-comes</td><td></td><td colspan="2">Adherence</td><td colspan="4">Nutrition/ Immune response</td><td colspan="3">Wound healing ⟶
Adherence ⟶</td></tr>
</table>

NS=nutrition support, NPO=nothing by mouth, ENT F/U=ear, nose & throat follow-up, prn=as needed, PGSGA=Subjective Global Assessment, RD=registered dietitian, RN=registered nurse
MN=midnight, LOS=length of stay, alb=albumin, prealb=prealbumin, DTH=delayed-type hypersensitivity testing

Measurement

Outcome measures were derived from the scientific literature where reports of studies involving immune-modulating nutrition helped with the selection of practical, useful measures for this pilot study.

Primary outcome measure: *Feasibility*

The rationale for looking at feasibility in this pilot study was that no studies had been conducted regarding preoperative or postoperative nutrition support for head and neck cancer patients in our facility. Generally, these patients, like most elective surgical patients, are admitted the day before surgery or the day of surgery and they have had little opportunity to improve their malnourished state since the preoperative consultation. Many patients reported symptoms of greater than 3 months duration and they were eating poorly, still smoking, and often drinking alcohol. Therefore it was important to determine if these patients would adhere to a preoperative nutritional regimen designed to improve their postoperative recovery.

Method of measurement: Descriptive.

The following questions and feasibility issues were monitored in order to determine whether a larger, multi-site, randomized clinical trial would be possible in the future. Issues of feasibility included subject recruitment and enrollment; exactly how many potential subjects were available to enroll in the protocol with the new VA initiative in place at our facility? This regional military medical center has entered into an arrangement with the local VA hospital to care for their beneficiaries in our facility using VA nurses

integrated into our nursing staff. How many of the eligible subjects will actually consent to participate? How many will remain in the study by adhering to the study procedures such as actually consuming the nutritional formula as prescribed, documenting additional oral intake in the diary, handling issues related to feeding devices, returning all containers used and unused, and following through with preoperative blood work, dietitian consultation, speech pathology consultation, and postoperative visits as directed? And how realistic is it to maintain a feeding tube in place for 7 days before surgery and 7 days after surgery if needed? Are temporary feeding tubes more acceptable than long-term PEG tubes? In addition to adherence issues, logistical issues such as specimen collection, processing, and reporting were examined, and close scrutiny of the selected assays and time points was conducted to determine the most significant intervals for measurement in the future. Physicians were required to input the required laboratory tests into the hospital computer system. Patients were instructed to report to the facility laboratory where baseline laboratory tests were drawn by trained phlebotomists. All other laboratory tests were drawn by unit phlebotomists or nursing staff after the patient was admitted for surgery and postoperative care. Prior to the study it was uncertain whether DTH skin testing could be reliably performed in intervals shorter than 2 weeks. Travel to and from the patient's home was monitored for frequency and cost and the impact this would have if personnel resources were not available in the future. Lastly, successful

management of the nutrition support regimen postoperatively by the nursing staff was examined. Artificial nutrition by feeding tube, and even the patient's oral diet, typically receives less attention in the nursing care plan than other activities related to healing.

Secondary measures: Nutritional outcome.

The rationale for examining nutritional outcome is simple; providing nutritional supplementation to undernourished cancer patients is expected to result in an improvement in visceral protein status, body weight, and surgical wound healing. Protein energy malnutrition is recognized as an important risk factor for the occurrence of postoperative complications. For this reason, nutritional support has been proposed as an essential part of perioperative care for malnourished surgical patients; either as oral supplements or tube feeding (FSSPEN, 1996).

Selected from numerous potential nutritional parameters to use in acutely ill or critically ill patients, biochemical assays of visceral proteins, albumin and prealbumin, provided important information regarding improvement in nutritional status over time related to the nutritional intervention. These values were examined twice (at baseline and day of surgery) over the 7 preoperative days to see if those patients who consumed the prescribed amount of nutritional supplement preoperatively could be distinguished from those who did not. Likewise, the values were examined to assess the adequacy of nutritional support in the 7 day postoperative period.

These biochemical assays are standard of care in monitoring nutrition support, the assays are readily available at most facilities, and they are relatively inexpensive to process. The Patient-Generated Subjective Global Assessment (PG-SGA) tool was used by the dietitian to assess baseline nutritional status and predict nutritional risk.

Method of Measurement: Biochemical assays

1) Albumin: An indicator of visceral protein depletion. Serum half-life of albumin is 28 days. Varying degrees of depletion correlate with morbidity and mortality in hospitalized patients. Normal level is 3.5-5.5 g/dL (MAMC Lab). Severe visceral protein depletion is demonstrated by serum albumin < 2.1 g/dL, moderate depletion is demonstrated by serum albumin 2.1-2.8 mg/dL, and mild depletion is seen with an albumin of 2.8-3.5 g/dL. Many variables can affect the reliability of this test as a measure of nutritional state; fluid status, use of corticosteroids, protein-losing states, acute infection, inflammation, and liver dysfunction (Cresci, 2002). Albumin trends are more indicative of a response to nutritional support. Several authors have shown a relationship between depressed serum albumin and postoperative infection and sepsis (Gibbs, Cull, Henderson, Daly, Hur & Khuri, 1999).

2) Prealbumin: A carrier protein involved with Vitamin A and thyroid hormone transport. Serum half-life of prealbumin is 2-3 days. Prealbumin is highly sensitive to dietary deprivation and refeeding so it is a useful indicator of response to nutritional therapy. It was measured upon entry into the study

and at four later time points. Normal level is 19-45 mg/dL (MAMC Lab). This protein marker with a shorter half-life than albumin has become a routine lab test used as an early marker for malnutrition and has been shown to correlate well with albumin levels and measures of nitrogen balance. Like albumin, this marker is less reliable in the acutely ill patient experiencing fluid resuscitation, an inflammatory process, or wound protein losses (Winkler, 2005).

Patient-Generated Subjective Global Assessment (Appendix C).

This tool is based on the original Subjective Global Assessment (SGA) but has been modified for use with oncology patients (Ottery, 1995). Baker et al. (1982) demonstrated that clinical assessment using the SGA is reproducible and valid as it correlates well with objective nutritional measurements and morbidity. In two studies two observers agreed in 81.4% and 91% of patients, this level of agreement beyond chance is termed "substantial" (Baker, Detsky, Wesson, Wolnan, Stewart, Whitewell, et al., 1982). Researchers in Australia compared the PG-SGA with the original SGA in seventy-one patients with cancer (Bauer, Capra & Ferguson, 2002). The PG-SGA score had a sensitivity of 98% and a specificity of 82% at predicting SGA classification. There was a significant difference in the median PG-SGA scores for each of the SGA classifications ($p < 0.001$), with severely malnourished patients having the highest score. Re-admission within 30 days of discharge was significantly different between SGA groups ($p = 0.037$). It was appropriate to use this tool in this study because the patients described their recent weight history, food

intake, symptoms, activities, and functional abilities. It was obtained from the Society for Nutritional Oncology Adjuvant Therapy and the Oncology Nutrition Dietetic Practice Group of the American Dietetic Association.

Secondary measures: Immunologic outcome.

The rationale for incorporating immunologic outcome into this study was that the literature suggests that the most measurable benefit of nutritional support, and perioperative nutritional support in particular, is a reduction of postoperative infectious complications. The radical neck dissection or modified neck dissection is a lengthy, extensive surgical procedure required by many head and neck cancer patients. Infectious complications arise at the surgical incision or in distant locations such as the lungs, the urinary tract, or the bloodstream. Wound complications are also common in this population and include dehiscence, fistula formation, or flap failure. It was hypothesized that enhancing the immune response with immune-modulating nutrition would lead to an improvement in the rate of wound and infectious complications and would be a substantial benefit to the patient. Immunologic outcome was determined using DTH skin testing, total lymphocyte count and lymphocyte subset counts, and C-reactive protein assay.

Delayed-type hypersensitivity (DTH) skin testing is a sensitive indicator of intact cellular immunity. A positive response to intradermal antigen injection requires uptake and processing of antigen by antigen-presenting cells, their interaction with CD4+ helper T cells, cytokine

production by T cells, and subsequent recruitment and activation of monocytes and macrophages. Certain immune defects are associated with characteristic patterns of lymphocyte subsets, yet lymphocyte populations may appear to be entirely normal even with clinical evidence of significant immune dysfunction. Conversely, as with total lymphocyte numbers, lymphocyte subsets may be profoundly altered by common infectious illnesses. For this reason DTH results should be considered in conjunction with lymphocyte counts and subsets (Bonilla, 2003). The T cell dependent immune system has been shown to have a role in the regulation of wound healing. Activated T lymphocytes recruit, expand, and activate fibroblasts primarily responsible for wound repair. Dietary arginine, as in the IMN formula, has been shown to up-regulate T cell activity and increase protein and collagen deposition in an experimental wound in a sample of elderly adults (Bonilla, 2003; Kirk, Hurson, Regan, Holt, Wasserkrug & Barbul, 1993).

C-reactive protein (CRP) – CRP is an acute phase protein that influences one or more stages of inflammation. A presumed major function of CRP is its ability to bind phosphocholine, thereby permitting recognition of foreign pathogens and phospholipid constituents of damaged cells. CRP may activate the complement system and/or bind to phagocytic cells, resulting in elimination of targeted cells by interaction with both humoral and cellular effector systems of inflammation. The rapidity of the response indicates that CRP is a component of the innate immune response (Kushner, 2004). Because

there is no single best laboratory test to reflect inflammation, the optimal use of acute phase protein measurements is to obtain several measurements and interpret them in light of the clinical context.

Method of Measurement: Immunologic tests.

Delayed-type hypersensitivity (DTH) skin testing – Cell-mediated immunity was assessed by DTH skin testing. In this facility three antigens are intradermally injected as an anergy panel. These antigens are tetanus, tuberculosis, and Candida. Manufacturer's recommendations are to apply the antigens to the forearm and read the response at 48-72 hours. A similar technique to that described by Tepaske et al. (2001) was used to assess response; it was measured in two perpendicular directions 2 days after the injection and then halved. The sum of the responses (mm) is used in the analysis. The response was evaluated at two times, at baseline prior to the nutritional intervention and POD 8. The baseline testing helped to distinguish grades of malnutrition among study patients. Testing on POD 8 was planned as a way to identify which patients had improved recovery of cell-mediated immunity following 14 days of nutritional supplementation. It was hypothesized that patients in the treatment group receiving IMN should have a normal (positive) DTH response indicating full recovery of cell-mediated immunity by POD 8 while patients receiving standard nutrition support may still be unable to mount a significant immune response following surgery. One potential problem with repeated measurement of DTH response could be that

the small amount of antigen in the first test might boost the response. However, this may make an observed deterioration in response more meaningful. The DTH response has been shown to correlate with clinical outcome in other studies; DTH response was a predictor of postoperative infectious morbidity in patients undergoing cardiac surgery, and improved DTH response was also found in major abdominal surgery patients on postoperative IMN (Tepaske et al., 2001)

Total lymphocyte count (TLC) and lymphocyte subsets – With regard to nutritional status, a TLC of 1500-1800 mm^3 reflects mild depletion; 900-1500 mm^3, moderate depletion; and < 900 mm^3, severe depletion (van Bokhurst-de van der Schueren et al.,1997; van Bokhurst-de van der Schueren et al.,1998). Lymphocytes and lymphocyte subsets were measured in fresh heparin-treated venous blood after erythrocyte lysis of whole blood samples. The absolute numbers and percentages of leukocytes and lymphocytes, the percentages of pan B lymphocytes (CD19), T lymphocytes (CD3+), T helper lymphocytes (CD4+), T suppressor lymphocytes (CD8+) and the CD4/CD8 ratio were reported. For analysis by flow cytometry, blood cells are mixed with fluorochrome-labeled monoclonal antibodies that bind to cell surface markers that distinguish various categories of lymphocytes. The flow cytometer detects fluorescence and counts the number of cells that bind the monoclonal antibody on their surface. Results were expressed as a percentage of cells analyzed.

T and B lymphocytes as well as lymphocyte subsets were measured at 5 time points; baseline prior to nutritional intervention, day of surgery, POD 1, 4, and 8. Baseline testing was used in conjunction with the nutritional assessment to categorize the degree of malnutrition preoperatively. Day of surgery testing was done to distinguish a positive effect of nutritional repletion after 7 days of feeding. Postoperative day 1 testing demonstrated the degree of surgical stress on circulating lymphocytes and lymphocyte subsets in both study groups. The acute-phase reaction and systemic inflammation after surgery typically resolves by 72 hours. Following a post-surgical immunosuppression, cell-mediated immune response measured by lymphocytes and lymphocyte subsets should be returning to normal levels and a measurement on POD 4 should reflect this metabolic transition. It was hypothesized that patients in the treatment group who received IMN would demonstrate a return to baseline lymphocyte counts and subset counts by POD 8 when compared to patients who received standard formula. Those who received standard formula were expected to demonstrate persistent abnormalities in lymphocyte counts and subset counts even after 14 days of nutritional support.

C-reactive protein was measured via serum assay at the same five time points as the nutritional and other immunologic biomarkers; baseline, day of surgery, POD 1, POD 4, and POD 8. The CRP assay required 6 mL of serum in a gold top tube for processing. For most clinical purposes, CRP values less than 0.1 or 0.2 mg/dL can be regarded as normal and values over 1.0 as

indicating clinically significant inflammation. Although CRP is a sensitive indicator of inflammation, it is not specific. Values greater than 0.2 and less than 1.0 mg/dL may reflect minor degrees of inflammation, but also reflect obesity, cigarette smoking, hypertension, low levels of physical activity, chronic fatigue, alcohol consumption, aging, periodontal disease, or depression (Kushner, 2004). Measurements of acute phase reactants, particularly CRP, can be a useful prognostic indicator for some patients with malignancy and elevations may indicate the presence or absence of tumor recurrence (Nozoe, Matsumata, Kitamura & Sugimachi, 1998).

Secondary measures: Wound healing.

The rationale for including wound healing as an outcome measure was that no previous studies involving IMN have included wound healing as a short-term outcome measure separate from infectious complications. It is unclear if nutritional status or immune status plays a greater role in postoperative complications. It is known that nutritional status prior to wounding impacts the healing process. Windsor et al. (1988) found that the preoperative food intake had a greater influence over the wound healing response than absolute losses of protein and fat from body stores. Their results in 83 general surgical patients suggested that maintenance of a normal food intake up until the time of surgery was important in preventing impairment in the wound healing response (Windsor et al., 1988). Malnutrition increases

postoperative mortality, morbidity, rehabilitation time, risk of infection, and it delays wound healing (van Bokhurst-de van der Schueren et al., 1997).

Method of Measurement: Visual assessment.

ASEPSIS scoring tool - Wounds were scored according to the ASEPSIS method; a scoring system that examines **A**dditional treatment, **S**erous discharge, **E**rythema, **P**urulent exudate, **S**eparation of deep tissues, **I**solation of bacteria, and **S**tay as inpatient prolonged over 14 days (Wilson, Sturridge, Treasure & Grunberg, 1986). Comparisons of the ASEPSIS method with standard clinical definitions of wound infection or complications demonstrated that ASEPSIS was as sensitive as and significantly more specific than the other indicators of wound problems (Wilson, Webster, Grunberg, Treasure & Sturridge, 1990). Reliability of the instrument is also high. Byrne et al. (1989) reported a correlation coefficient for two observers of 0.96 and a coefficient of repeatability of 3.4 in patients undergoing general surgical procedures (Byrne, Malek, Davey & Cuschieri, 1989). Previous data from vascular surgery patients demonstrated that individuals with an ASEPSIS score of 11-20 points (i.e. minor disturbance in healing) had a median length of stay of 12 days compared to those with an ASEPSIS score of 0-10 points (i.e. normal healing) and a median length of stay of only 8 days ($p < 0.001$). Similarly, those patients with scores higher than 20 points stayed longer than those with scores between 11 and 20 points ($p< 0.04$). These data support the

concurrent validity of the ASEPSIS tool (Wipke-Tevis, Stotts, Skov & Carrieri-Kohlman, 1996).

Using the ASEPSIS method, the wound site was evaluated on 4 major characteristics (serous exudate, erythema, purulent exudate, and separation of deep tissues). The proportion of the wound that demonstrates one or more of the characteristics is assigned a numerical score (Appendix E. ASEPSIS Tool). For example, purulent exudate and separation of deep tissues is scored from 0 to 10 (0=no part of the wound affected, 10=more than 80% of the wound affected). Scores for each characteristic were summed with the range of possible scores being 0-40. An additional one-time score was assigned based on the presence or absence of the following: additional treatment (antibiotics, drainage, and/or debridement of the wound under anesthesia), isolation of bacteria, and inpatient stay more than 14 days. The total score indicates the severity of wound infection (i.e. 0-10 = satisfactory healing, 11-20 =disturbance of healing, 21-30 = minor wound infection, 31-40 = moderate wound infection, >40=severe wound infection). Prior to beginning the study interrater reliability was established between the two experts (Whitney, Heiner, Mygrant & Wood, 2001).

Wound assessment, inspecting the wound visually, was performed by two qualified health care professionals (surgeon and the nurse investigator), who were blinded to patient treatment group, every day postoperatively until discharge and then at weekly intervals for a total of 3 weeks using the

ASEPSIS method. Photographic images of the surgical incision were taken on POD 1, 4, and 8 and at clinic follow-up visits by the nurse investigator using a medical quality Polaroid Spectra® camera (Briggs Corp.). The hospital CWOCN nurse was experienced at wound photography and taught the investigator the proper techniques. The Polaroid photos were used for intra- and interobserver reliability testing using the first few subjects enrolled in the study and again halfway through subject recruitment. Photos provided a reliable historical reference because they are not alterable like digital photos.

Study-Specific Instruments

Demographic data collection tool (Appendix B).

An 18-item tool was created to compile demographic information from each study participant. It was used to compare participants at baseline from the two groups. Specific demographic information obtained included age, gender, date of birth, diagnosis, tumor stage, prior surgical history, prior radiation history, date of surgery, planned preoperative placement of feeding tube/PEG tube, height, weight, ideal body weight, body mass index, and admission weight.

Daily nutritional intake tool (Appendix F).

This tool was created to annotate the patient's postoperative daily intake of study formula or other oral intake as well as reasons why no intake occurred e.g. clogged feeding tube, vomiting, or hold status for a procedure. The amount of formula received versus prescribed and the percent of

nutritional goal attained have been used by other researchers to explain why some patients seemed to benefit from the nutritional product and others did not. As with almost any intervention study, knowledge of the intervention strength or "dose" is necessary for valid interpretations of outcomes (Sidani & Braden, 1998).

Methods of Analysis

All statistical analyses were done using Statistical Package for the Social Sciences (SPSS) version 12 for Windows. Descriptive statistics were used to describe the characteristics of study participants. Frequency distributions (number and percent) summarized risk factors, type of tumor, prior surgery, prior radiation, and staging. Means, standard deviations, and ranges summarized age and baseline nutritional and immunologic biomarkers. The following approach to the data analysis addressed the specific aims in a step-wise fashion.

Specific aim #1. To evaluate the feasibility of providing perioperative nutritional support to a convenience sample of undernourished adults undergoing surgery for head and neck cancer in a regional military medical center.

According to Sidani and Braden (1998) client characteristics result in individual differences in the outcome variables. These differences can lead to a) large between-group differences that are not causally linked to the

intervention and therefore induce bias in estimating the intervention effects, and b) increased individual variability in the outcome that weakens the statistical power to detect significant intervention effects and that limit the generalizability of the findings. Consequently, client characteristics present alternative explanations of the study findings, whether the findings are significant or not. Client characteristics were described in detail for the specific aim of feasibility.

The recruitment and retention of study participants and the investigator's record of challenges implementing the intervention are included as part of the discussion of feasibility. The number of potential participants recruited and the number and percent of participants who completed the program and all follow-up measures summarized recruitment and retention of participants. Reasons for attrition were documented to evaluate for common issues. The investigator's log maintained descriptions of problems with study procedures or intervention delivery.

Specific aim #2. To compare the difference in the nutritional parameters, albumin and prealbumin, between undernourished adult patients receiving IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

An independent t-test using nutritional parameters (albumin, prealbumin) was performed for Baseline, Day of Surgery, POD 1, POD 4, and POD 8 to compare means between the two groups. The Patient-Generated

Subjective Global Assessment tool was used to evaluate the patient's nutritional status at baseline and predict nutritional risk and then compare the scores between groups.

Specific aim #3. To compare the difference in immune response measured by delayed-type hypersensitivity skin testing, lymphocyte counts, lymphocyte subset counts, and C-reactive protein between undernourished adult patients randomized to receive either IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

Statistical analysis to compare the two groups for immune response (total lymphocytes, CD3, CD4, CD8, CD4/CD8, CD19, CD56, and CRP) included mean $\pm$ SD, and analysis of covariance using baseline lab values as the covariant. The delayed-type hypersensitivity testing response was reported as a measurement in millimeters with an independent t-test performed between groups at baseline and POD 8.

Specific aim #4. To compare the difference in surgical wound healing measured by visual inspection between undernourished adult patients randomized to receive either IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

Wound healing outcome between groups was examined by t-test comparing ASEPSIS scores on selected days.

Chapter Four Results

Introduction

This chapter presents the results of the study "Perioperative Immunonutrition for Head and Neck Cancer: A Feasibility Study." This pilot study examined feasibility as its main outcome measure and nutritional, immunologic, and wound healing outcomes as its secondary measures. The first section describes the sample population including demographic and tumor characteristics. The following sections present the results of the study addressing the four specific aims. Results related to feasibility of the intervention include summaries of participant recruitment, intervention delivery, and technical/logistical issues. Results of the exploratory analyses of intervention effects for the secondary aims are also presented.

Description of the Sample Population

A summary of the sample demographics and tumor characteristics is included in Table 6. Participants were 12 Caucasian males with a mean age of 60.8 years (SD $\pm$ 8.3, range 46-73) diagnosed with a head and neck cancer. All patients had received their diagnosis within the week of contact by the investigator and were scheduled for surgery 7 to 14 days later. For four patients this diagnosis represented a second or recurrent cancer diagnosis. These four patients had received radiation previously, one received chemotherapy in the past as well, and three had undergone surgery for a previous cancer. Three had previous head and neck cancers and one had

prostate cancer. The remaining eight participants had not received radiation or chemotherapy prior to this scheduled surgery. The most common tumor site was the oropharynx, which includes the floor of the mouth, the tongue, and the tonsils (66.7%), followed by the larynx (25%), and hypopharynx (8.3%). These sample statistics are comparable to national statistics although this sample was slightly younger (60.8 yrs vs 65 yrs) than most reports in the literature (Ries et al., 2004).

Tumor stage was dispersed among all four stages but 58.4% were of the most advanced stages, III and IV. The majority of patients (n = 10) reported difficulty breathing, swallowing, or eating, as well as a decline in physical stamina. Delays in seeking medical attention for these complaints were common and reasons given included getting their affairs in order, denial that there was anything wrong, denial that another tumor could have developed, and awaiting information on medical benefits from the Veteran's Administration. The literature reports that despite obvious and common complaints, two out of three patients with head and neck cancer present at an advanced stage, due to neglect on the part of the patient, but also due to a delay in diagnosis (Shaha, Patel, Shasha & Harrison, 2001).

Nutritional assessment upon entry into the study revealed that the sample was generally just below ideal body weight (M 94.6% $\pm$ 12.9; range 69 – 120%), body mass index was normal for most participants (M 22.8 $\pm$ 3.5; range 15.5 – 28.5, normal 20-25), and the mean percent weight loss in the

range 15.5 – 28.5, normal 20-25), and the mean percent weight loss in the previous 6 months was 9.8% (SD ± 9.1; range 0-32%). Mean height of the sample was 67.8 inches (SD ± 2.1; range 64-72 inches) and mean weight was 154.7 pounds (SD ± 24.6; range 100-185 lbs). The Patient-Generated Subjective Global Assessment was used by the dietitian to score patients as (1) well-nourished, (2) moderately malnourished, or (3) severely malnourished. The mean score for all patients was 1.67 (SD ± .65); only one patient was considered severely malnourished. Patients were asked to maintain a diary and record the amount of nutritional supplementation consumed each day. Diary entries and personal conversations with patients and their spouse revealed that both groups consumed approximately 75% or greater of the prescribed supplement.

Table 6. Sample demographic and tumor characteristic, n=12

Characteristic	N	Percent	M (SD)
Age (years)			60.8 (8.3)
Gender Male	12	100.0	
Racial/Ethnic Group			
White	12	100.0	
Hispanic	0		
Asian, Pacific Islander	0		
Black, African-American	0		
American Indian	0		
Tumor Location			
Oropharynx/Tonsils/ Tongue	8	66.7	
Floor of mouth	1	8.3	
Hypopharynx	3	25	
Larynx			
Tumor Stage I	4	33.3	
II	1	8.3	
III	2	16.7	
IV	5	41.7	
% Weight Loss in 6 mo			9.8 (9.1)

 Table 6. (Continued)

% Ideal body weight			94.3 (14.2)
Body Mass Index			22.8 (3.5)
History of Alcohol Abuse Yes	11	91.7	
No	1	8.3	
History of Tobacco Use Yes	10	83.3	
No	1	8.3	
Current Employment Status			
Employed full-time or part-time	9	75.0	
Retired	3	25.0	

Specific Aim #1: Feasibility of providing perioperative nutrition supplementation to undernourished head and neck cancer patients

Recruitment and retention of participants.

Participant recruitment for the study took place between August 2004 and December 2005. It was initially anticipated that recruitment would take place over a 12 month period with each patient being followed for approximately 30 days. The investigator inquired about the annual number of cases of head and neck cancer undergoing elective surgery prior to developing the protocol. For the previous 2 years the number of cases averaged 16-20 which was acceptable for a pilot study. Once the study began it was obvious that recruitment and enrollment would be slower than expected due to fewer referrals than in previous years. The study was extended for 4 months. Quarterly recruitment occurred as follows:

Aug-Sept 04: 1 participant

Jan-Mar 05: 2 participants

Apr-Jun 05: 1 participant

Jul-Sept 05: 2 participants

Oct-Dec 05: 4 participants

Even though recruitment was slow no changes were made to broaden the inclusion criteria because almost all eligible study patients were being referred to the investigator. Two patients with laryngeal cancer were not referred to the investigator due to the Head and Neck Service Resident's lack of familiarity with the protocol. One patient was referred but was not eligible because it was a recurrence of his same tumor in a 6 month period of time. The study team agreed that it would be best not to re-enroll this subject as he had previously participated.

Twelve eligible individuals volunteered to participate in the study following screening for the inclusion criteria. In the 16 month period only two individuals contacted by phone declined to participate; one patient citing that the cancer diagnosis was already too much to worry about and the other stated the inconvenience of returning to the hospital on multiple occasions was a deterrent. Of the twelve volunteers three individuals were unable or unwilling to complete the preoperative nutritional supplementation. One patient experienced significant airway compromise that resulted in immediate surgery. This airway compromise was due to the enlarging tumor and was not related to

study participation. Another patient inadvertently received a tube feeding formula as an oral supplement and withdrew himself from the study citing unpalatability and nausea, and the third patient stated that the formula caused his diabetes to become uncontrolled with widely varying blood sugar readings. He discontinued the supplementation without informing the investigator, therefore evaluation and validation of his blood sugar concerns was not possible. Data for these patients were retained in the database in order to conduct intent-to-treat analyses. (Refer to Figure 2 for complete enrollment).

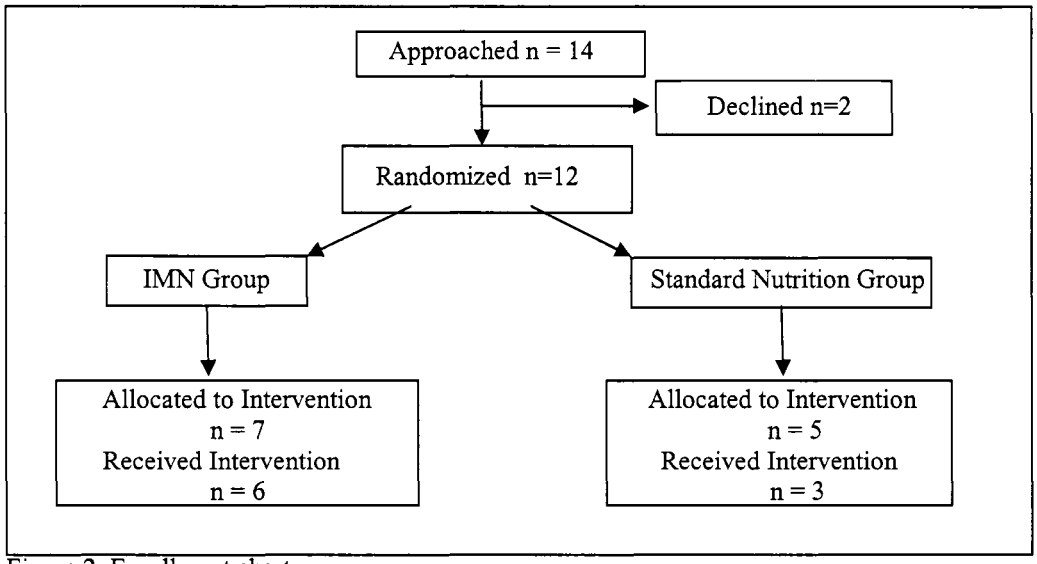

Figure 2. Enrollment chart

Intervention delivery.

Of the twelve patients enrolled in the study, 9 completed almost all study measures from baseline to week 3 follow up. The three other patients were unavailable for study measures at time points that occurred following

discharge and before the next follow-up appointment. No provisions were made to obtain biochemical tests at home following discharge. The postoperative protocol was based on historical data showing that head and neck cancer patients typically remained hospitalized for 7-10 days following surgery. It was not practical or fiscally sound to keep patients hospitalized longer than necessary just to complete the protocol. Nutritional supplementation continued at home after discharge without difficulty until postoperative day 8. At this time patients began a standard tube feeding formula or advanced to other oral intake. No patient requested a home visit after discharge as most issues were handled at the next follow-up appointment, usually within 5-7 days. Most patients were contacted within 2-3 days of discharge by the investigator just to check on their progress. All patients were provided with a list of contact phone numbers and several did call the investigator with concerns about swallowing, pain, and ordering supplies. If necessary, patients were instructed by the investigator to return to the clinic to see their surgeon sooner than scheduled for a "walk-in" visit. The concerns of the patient were then relayed to the surgeon. The issue of ordering additional supplies was handled with the assistance of a Social Worker at the facility.

Phone calls to the patients were planned for each day of the preoperative protocol which consisted of the 7 days immediately preceding surgery. The research assistant discussed a convenient time for the phone call or the initial visit with the patient. However, the research assistant had some

difficulty reaching patients on all 7 days. The purpose of the call was to answer questions and remind the patient to consume the prescribed amount of supplement. Calls only lasted about 5 minutes each day. Patients did not forget to take the supplement but did report that it was difficult to take 4 or 5 packets/cans of the supplement some days due to time constraints and personal commitments. Patients had a low rate of returning their diaries or their empty and /or unused packets and cans of formula. Four of the twelve patients returned empty packets, no unused formula was returned. Ten patients received the diary and instructions and six of the ten returned completed diaries (60%). Examples of comments and questions written in the patient's diaries include: 1) "When you start the feeding tube can you still use the ice cream, how thick can it be?" (Patient 03), 2) "Was surprised it tasted so good. I could get to really like it (coffee flavor). Maybe want to stay on it." (Patient 01), 3) "Very filling. Want to know what I weigh." (Patient 01), 4) "This tastes so bad that I know I can be on the reality show –Fear Factor." (Patient 04).

Study participants were not formally asked to evaluate the various aspects of the study that impacted their time or their daily activities. There was no mention of feeling burdened by study procedures such as phone calls, laboratory tests, specialty consultations, visits by the investigator while hospitalized, or wound photographs. In fact, patients more often expressed gratitude for the additional measures taken by the multidisciplinary team to promote the best surgical outcomes for them. The special attention given to

individual concerns was greatly appreciated by patients and their family members. Several patients phoned the investigator following their discharge to say thank you or to ask for assistance with an issue they did not know how to resolve. The investigator served these patients as a patient advocate and assisted patients with many post-discharge needs such as procuring nutrition formula for home use via the Veteran's Administration, coordinating additional follow-up appointments with the surgeon or dietitian, providing education about gastrostomy tubes, radiation, or chemotherapy, and offering advice for comfort measures related to oral pain. Patients who underwent a total laryngectomy were invited to participate in a Laryngectomee Support Group that met monthly.

It is the opinion of the entire study team that the majority of patients demonstrated a commitment to following the protocol. Several patients reported that they had consumed all or nearly all of their supplements. There is little hard evidence to support this without all the diaries and empty containers; 6 patients returned diaries. Some patients requested to exchange packets for flavors that appealed to them more and the investigator took this as an indication that patients were at least trying to follow instructions to consume 4 or 5 packets a day. The choice to participate in a research study provided an opportunity for patients to actively engage in a simple dietary measure that could increase their chances of a smooth, uneventful recovery from a major operation.

Summary of Results Addressing Specific Aim #1.

In summary, recruitment proceeded more slowly than anticipated but was determined by the referrals to the Otolaryngology, Head and Neck Service. This resulted in an insignificant 4 month extension of the protocol. There was a high level of retention of study participants; 3 did not complete the preoperative protocol and only available measurements were included in the study. Occasionally biochemical measurements for patients were missing at designated time points due to physicians forgetting to order the lab tests, lab tests falling on a weekend meant no technician was available to run the specimen, and early discharge of the patient. The initial meeting with patients who volunteered to participate was more thorough and productive when it took place in the hospital rather than at the patient's home. Daily phone calls were brief, if the RA was successful in reaching the patient. Only half of the patients remembered to return diaries or empty packets/cans when being admitted for surgery. This was partly due to the lack of reinforcement of this aspect of participation by the study RA. The investigator was available to the family members at all times to answer general questions, explain procedures, and provide information about care after discharge. There is no question that an intervention study for patients with head and neck cancer such as this is feasible and practical with minimal burden to patients and staff. The investigator was unfamiliar with typical presenting complaints of this patient

population and reconsideration of initial plans for nutritional measurements became necessary once the study was underway.

Specific Aim #2: To compare the difference in the nutritional parameters between adults receiving IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

Nutritional parameters.

After examining the data for outliers an independent samples t test was performed using baseline albumin and prealbumin, DOS albumin and prealbumin, POD 1 albumin and prealbumin, POD 4 albumin and prealbumin, and POD 8 albumin and prealbumin. The baseline albumin for the experimental group (M = 4.01; SD $\pm$ .51) and the control group (M = 3.58; SD $\pm$ .96) were not statistically different (p = .33). The baseline prealbumin for the experimental group (M = 22.3; SD $\pm$ 8.6) and the control group (M = 12.8; SD $\pm$ 4.1) were also not statistically different (p = .13). While there was no statistically significant difference found between groups in albumin or prealbumin from baseline to DOS, POD 1, POD 4, and POD 8, the difference in albumin on POD 4 between groups approached significance with p = .06 and the difference in prealbumin on POD 4 between groups demonstrated a similar trend (p = .07).

Table 7. Albumin and prealbumin over time

Visceral protein	Group	Baseline	Day of surgery	POD 1	POD 4	POD 8
Albumin (nl 3.5-5.5 mg/dL)	Experimental	4.01	2.43	2.58	3.12*	3.15
	Control	3.58	2.90	2.02	2.26*	2.83
Prealbumin (nl 19-40 mg/dL)	Experimental	22.3	15.6	13.7	14.5*	14.3
	Control	12.8	14.5	9.2	8.63*	10.9

*approached significance

Patient-Generated Subjective Global Assessment.

Patient-generated subjective global assessment (P-GSGA) score was used to assess the patient's current nutritional status and to assign a level of nutritional risk based on the extent of the impending surgery, the plan for radiation and/or chemotherapy, the current barriers to adequate nutrition, and the recent measurement of visceral protein stores (albumin, prealbumin). A licensed hospital dietitian performed the assessment using the P-GSGA tool preoperatively for all patients. The tool uses a scoring system of 1 to 3 where a score of 1 means 'well-nourished", 2 means "moderately malnourished" and 3 means "severely malnourished". Assessment for the experimental group ($M = 1.57$; $SD \pm .54$) and the control group ($M = 1.8$; $SD \pm .84$) revealed no difference in baseline nutritional status ($p = .57$) with all patients assessed as being between moderately malnourished and well-nourished.

Nutrition risk scores were based on a 0 through 3 rating with 0 meaning "no nutritional risk" and 3 meaning "severe nutritional risk". Baseline risk assessment scores for the experimental group ($M = 2.29$; $SD \pm .49$) and for the control group ($M = 2.20$; $SD \pm .84$) were not significantly different ($p = .83$).

However, the scores of 2.20 and 2.29 suggested that the majority of patients were at a moderate to high risk for nutritional deficits related to their planned surgery, underlying diagnosis, and current nutritional status.

Summary of Results Related to Specific Aim #2.

It was stated from the beginning of this study that any analyses on secondary outcomes would be exploratory in nature as this pilot study was not powered to detect group differences. It was reassuring to see that recovery of the acute phase reactants, albumin and prealbumin, was not impaired in either group and levels were returning toward baseline by POD 4. This is when the inflammatory response should be subsiding and an augmented nutritional status should promote a positive shift in acute phase reactants towards protein anabolism (Cresci, 2002). Since both groups did receive supplemental nutrition this could be a reflection of simply an improved nutritional state going into surgery.

The patient-generated subjective global assessment was an excellent tool to identify the patient's current nutritional status and to provide insight into their nutritional risk based on the proposed plan for surgery. However, having observed these patients for over a month following surgery it was easy to see that the tool did not accurately predict the extent of eating difficulties and weight loss that most of the patients experienced. Nutritional risk may need to be assessed before and after surgery as the deficits related to

postoperative swallowing dysfunction, radiation, and chemotherapy were often underestimated.

Specific aim #3. To compare the difference in immune response measured by delayed-type hypersensitivity skin testing, total lymphocyte counts, lymphocyte subset counts and c-reactive protein between undernourished adult patients randomized to receive either IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

Delayed–type hypersensitivity (DTH) skin testing.

DTH skin testing was selected as a measure of immune response because of its easy application, frequent use as an immune marker, and its ability to provide important information regarding an individual's cell-mediated response. The immunization clinic staff was contacted prior to including this measure and assured the investigator that it would be no problem to place the DTH skin test or anergy panel consisting of tetanus, tuberculosis, and candida on the forearm of 12 subjects at two time points approximately 2 weeks apart. However, obtaining this anergy panel was more difficult than anticipated. The immunization clinic has very strict hours of operation which limited their availability for the baseline/pre-intervention test; they were closed during the lunch hour and on holidays and military training holidays (usually Mondays and Fridays), they have long waiting times for non-urgent testing, and they insist on reading the result in 48 hours which eliminated Thursdays and Fridays for testing. Patients who received the DTH skin test pre-

intervention were most likely to follow through with obtaining it post-intervention. Another reason that post-intervention testing was not successful was that patients who had been discharged prior to POD 8 did not want the additional trip back to the hospital for the skin test and then again 48 hours later for the reading. If a patient was still in the hospital on POD 8 they were often too sick to be transported to the Immunization Clinic where they might wait for 30-60 minutes to be seen. One solution for the reading of the DTH skin test that was placed on a Thursday or Friday pre-intervention, was to have the RA trained, according to Immunization Clinic policy, to read the test properly so this could be done at the patient's home. This was successful with three patients. Two of the three patients who did not fully complete the pre-intervention measures also did not obtain the DTH skin test; one was hospitalized emergently and one enrolled in the study on a Thursday. Reading the result on the weekend was not possible because of staff unavailability. Two other patients lived between 60 and 200 miles from the facility and home visits or return visits to the hospital were difficult to arrange. Lastly, there was no convenient time to arrange the skin test for two patients and one patient refused. Overall, 5/12 patients or 42% completed the pre-intervention DTH skin test and 2/12 or 17% completed the post-intervention DTH skin test.

The investigator was particularly interested in the pre-intervention test results because the DTH skin test can also be used to validate a state of malnutrition. Patients that are unable to mount a measurable response to the

DTH skin test are commonly malnourished, although many factors such as medications can affect response to the skin test. The small number of patients who received the skin test did not provide a sufficient sample on which to test the hypothesis that the experimental treatment group would demonstrate a more robust response to the skin test than the control group following 2 weeks of nutritional supplementation with an immune-modulating formula. The group of patients who did receive the pre-intervention skin test had a mean weight loss of 4%, received a mean subjective global assessment score of 1 or "well-nourished", and had a calculated nutritional risk of 2 or "moderate nutritional risk". Baseline mean total lymphocyte count for this small group of patients was low normal, M = 1650 mm^3, SD $\pm$ 637, range 1300-2500 mm^3. Normal total lymphocyte count at the MAMC lab is 900-3000 mm^3. This small sample did not appear to be significantly malnourished upon entry into the study based on the combination of DTH skin test results, weight loss, PG-SGA score and lymphocyte count. Total lymphocyte count less than 1500 mm^3 is suggestive of malnutrition.

Total lymphocyte count and lymphocyte subset counts.

Baseline experimental group mean TLC was 1800 mm^3 (SD$\pm$ 568) and baseline control group mean TLC was 1275 mm^3 (SD $\pm$ 689). An independent samples T test comparing the baseline means for total lymphocyte count (TLC) indicates that the groups were not significantly different upon entry into the study; t =1.37, df = 9 and p = .20. The initial group differences most likely

reflect chance sampling fluctuations. The post-surgical means show expected downward trends with a mean TLC on POD 1 for the experimental group of 942/mm^3 and 1000/mm^3 for the control group, and on POD 4 the experimental group mean TLC was 1100/mm^3 and the control group mean was 1000/mm^3. On POD 8, the final measurement interval, mean TLC for the experimental group was 1320/ mm^3 and for the control group, 1187/mm^3. The differences on POD 4 were not statistically significant $t = .54$, $df = 7$, and $p = .61$. Likewise, the differences on POD 8 were not statistically significant $t = .52$, $df = 6$, and $p = .66$ (equal variances not assumed because $F < .05$). Both groups were returning to baseline values by POD 8.

Table 8. TLC – Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	F	Sig.	t	df	Sig. (2-tailed)	Mean Diff	Std. Error Diff	Lower	Upper
baseline lymphs	.13	.725	1.369	9	.204	.525	.38	-.342	1.4
DOS lymphs	.06	.821	.381	5	.719	.190	.50	-1.1	1.5
POD1 lymphs	1.2	.310	-.181	8	.861	-.06	.32	-.786	.67
POD4 lymphs	1.6	.252	.540	7	.606	.100	.19	-.338	.54
POD8 lymphs	.03	.865	.520	6	.622	.133	.26	-.495	.76

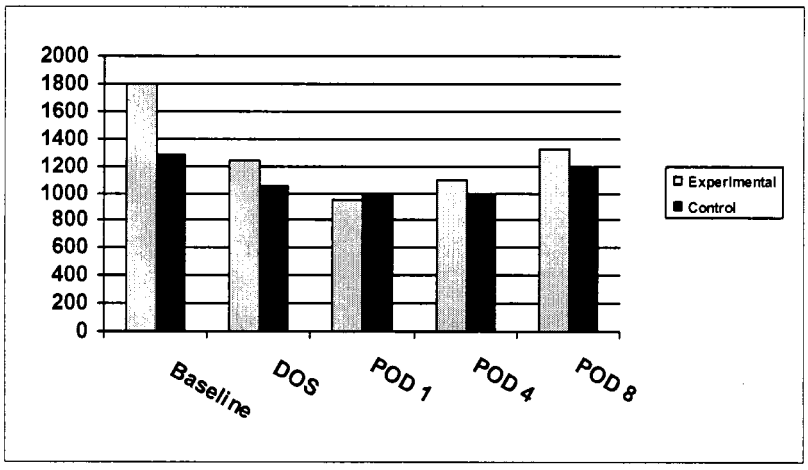

Figure 3. Total Lymphocyte Count

The hospital's standard panel for lymphocyte subsets included CD 3 (T cells), CD 4 (T helper/inducer cells), CD 8 (T suppressor/cytotoxic cells), CD 19 (B cells), CD 56 (natural killer cells), and a CD 4:8 ratio. Table 9 lists descriptives for the lymphocyte subsets. An analysis of variance between groups was performed for the lymphocyte subset counts at baseline (Day 0) and on Day of Surgery, POD 1, POD 4, and POD 8.

Table 9. Group statistics for lymphocyte subsets

		Mean	Std Deviation	Std Error
Baseline CD 3/mm^3	Experimental	1193.00	443.96	221.98
	Control	906.00	577.30	288.65
Baseline CD 4/mm^3	Experimental	716.25	347.42	173.71
	Control	368.50	382.36	191.18
Baseline CD 8/mm^3	Experimental	450.25	175.27	87.64
	Control	465.50	251.12	125.56
Baseline CD 4:8/mm^3	Experimental	1.69	.79	.39
	Control	.90	.70	.35
Baseline CD 19/mm^3	Experimental	240.25	101.25	50.62
	Control	100.75	52.92	26.46
Baseline CD 56/mm^3	Experimental	225.50	94.46	47.23
	Control	154.25	52.56	26.28
DOS CD 3/mm^3	Experimental	882.50	379.71	268.50
	Control	490.00	*	*
DOS CD 4/mm^3	Experimental	383.00	213.54	151.00

Table 9. (Continued)

	Control	249.00	*	*
DOS CD 8/mm^3	Experimental	464.50	168.99	119.50
	Control	234.00	*	*
DOS CD 4:8 /mm^3	Experimental	.79	.169	.120
	Control	1.06	*	*
DOS CD 19/mm^3	Experimental	202.00	233.34	165.00
	Control	132.00	*	*
DOS CD 56/mm^3	Experimental	99.50	24.74	17.50
	Control	110.00	*	*
POD 1 CD 3/mm^3	Experimental	787.00	241.94	139.68
	Control	851.00	35.35	25.00
POD 1 CD 4/mm^3	Experimental	422.00	209.00	120.66
	Control	424.00	42.42	30.00
POD 1 CD 8/mm^3	Experimental	346.00	160.39	92.60
	Control	383.00	15.55	11.00
POD 1 CD 4:8 /mm^3	Experimental	1.39	.96	.55
	Control	1.11	.15	.11
POD 1 CD 19/mm^3	Experimental	207.33	115.32	66.58
	Control	271.00	258.80	183.00
POD 1 CD 56/mm^3	Experimental	119.66	32.80	18.94
	Control	86.50	13.43	9.50
POD 4 CD 3/mm^3	Experimental	859.00	114.00	57.00
	Control	705.66	440.00	254.03
POD 4 CD 4/mm^3	Experimental	463.00	202.58	101.29
	Control	281.66	306.00	176.67
POD 4 CD 8/mm^3	Experimental	363.50	133.58	66.79
	Control	342.33	141.00	81.40
POD 4 CD 4:8 /mm^3	Experimental	1.58	1.26	.63
	Control	.86	.73	.42
POD 4 CD 19/mm^3	Experimental	146.25	52.04	26.02
	Control	86.00	51.68	29.83
POD 4 CD 56/mm^3	Experimental	138.50	60.89	30.44
	Control	86.66	79.56	45.93
POD 8 CD 3/mm^3	Experimental	1148.00	437.13	218.56
	Control	940.33	452.56	261.28
POD 8 CD 4/mm^3	Experimental	634.50	272.58	136.29
	Control	586.66	363.44	209.83
POD 8 CD 8/mm^3	Experimental	476.50	215.06	107.53
	Control	540.00	371.20	214.31
POD 8 CD 4:8 /mm^3	Experimental	1.53	.91	.45
	Control	.81	.60	.35
POD 8 CD 19/mm^3	Experimental	149.50	27.08	13.54
	Control	75.33	13.20	7.62
POD 8 CD 56/mm^3	Experimental	173.25	162.19	81.09
	Control	165.33	69.55	40.15

Table 10 shows by ANOVA that the two groups were not significantly different for any lymphocyte subset except CD 19/mm^3 at baseline and POD 8.

Counts for both groups were within normal limits (45-337/mm^3) but the experimental group demonstrated a higher mean count of CD19 cells (M = 240.25 vs 100.75/mm^3; p = 0.05) at baseline and on POD 8 (M = 149.5 vs 75.3 /mm^3).

Table 10. ANOVA of lymphocyte subsets

Subset classification	Measurement Interval	F statistic	p value
CD 3	Baseline	.621	.46
	DOS	.712	.55
	POD 1	.125	.74
	POD 4	.473	.52
	POD 8	.376	.56
CD 4	Baseline	1.81	.22
	DOS	.263	.69
	POD 1	.000	.99
	POD 4	.900	.38
	POD 8	.040	.84
CD 8	Baseline	.010	.92
	DOS	1.24	.46
	POD 1	.095	.77
	POD 4	.041	.84
	POD 8	.083	.78
CD 4:8	Baseline	2.22	.18
	DOS	1.68	.41
	POD 1	.156	.71
	POD 4	.75	.42
	POD 8	1.34	.29
CD 19	Baseline	5.96	.05*
	DOS	.06	.84
	POD 1	.15	.71
	POD 4	2.31	.18
	POD 8	18.49	.008*
CD 56	Baseline	1.73	.23
	DOS	.12	.78
	POD 1	1.69	.28
	POD 4	.968	.37
	POD 8	.006	.94

* statistically significant, p $\geq$ 0.05

After evaluating the data for correlations between baseline subset values and all subsequent subset values, the ANOVA procedure was followed

by an analysis of covariance (ANCOVA). This technique involves the regression of the dependent variable (individual lymphocyte subset) on the selected covariate (baseline lymphocyte subset) to determine if any variance in post-intervention lymphocyte subset count is accounted for by the covariate. The baseline (Day 0) lymphocyte count was selected as the covariate and lymphocyte count on the respective intervals (DOS, POD 1, POD 4, and POD 8) was the dependent variable with group assignment as the independent variable. The stronger the correlation between the covariate and the dependent variable, the better is the covariate. When correlations were tested between baseline lymphocyte subset count and subsequent counts correlations were generally high with exceptions on POD 1 for CD19, CD8, and CD4:8 ratio and POD 8 for CD3 and CD4. All other measurement intervals for lymphocyte subsets demonstrated correlations with the covariate between .559 and 1.00.

Based on the results of the ANCOVA procedure and after controlling for the baseline lymphocyte subset count, there is an indication that CD56 natural killer cell count on POD 1 was the only subset that demonstrated a statistically significant difference in post-intervention counts. CD56: $F = 49.05$, $df = 1,2$, $p = .02$, Partial Eta squared = .96. It is important to point out that the Levene's Test for Equality of Variance was performed and the p value for the Levene F statistic was not significant. This means there is no evidence for heterogeneity of variance. A non-significant Levene Statistic for the Test

for Homogeneity of Variances was achieved for all subsets except for CD4 on POD 4 and CD56 on POD 4.

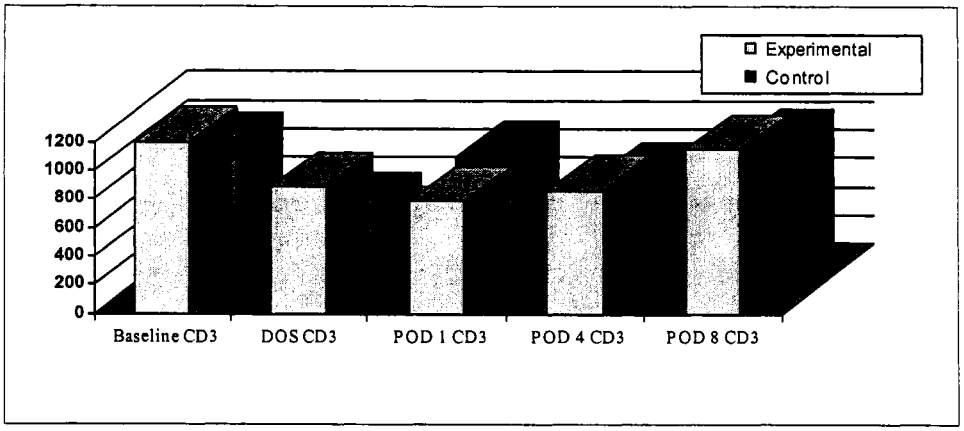

Figure 4. CD3 Counts

Tables 11 through 28 display ANCOVA results. If the effect of the covariate resulted in an F statistic significant beyond the .05 level the ANCOVA table shows this value along with the p value and effect size or partial Eta squared. Otherwise only the main effect of the group after the covariate was removed is displayed.

Table 11. ANCOVA for CD3
Dependent variable: POD 1 CD3/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	2230.62	1	2230.62	.05	.84	.024
Error	88989.21	2	44494.60			
Corrected total	123239.20	4				

Table 12. ANCOVA for CD3
Dependent variable: POD 4 CD3/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
baseline CD3	324684.58	1	324684.58	**11.49**	**.043**	**.793**
group	36194.05	1	36194.05	1.28	.34	.299
Error	84784.74	3	28261.58			
Corrected total	429653.33	5				

Table 13. ANCOVA for CD3
Dependent variable: POD 8 CD3/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	21633.55	1	21633.55	.089	.78	.029
Error	731076.60	3	243692.20			
Corrected total	851996.83	5				

Table 14. ANCOVA for CD4
Dependent variable: POD 1 CD4/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	1078.41	1	1078.41	.046	.85	.023
Error	46608.85	2	23304.42			
Corrected total	89166.80	4				

Table 15. ANCOVA for CD4
Dependent variable: POD 4 CD4/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
baseline CD4	244719.32	1	244719.32	**12.19**	**.04**	**.803**
group	14533.51	1	14533.51	.724	.45	.194
Error	60224.01	3	20074.67			
Corrected total	366554.00	5				

Table 16. ANCOVA for CD4
Dependent variable: POD 8 CD4/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	2206.97	1	2206.97	.018	.90	.005
Error	373347.38	3	124449.13			
Corrected total	378889.33	5				

Table 17. ANCOVA for CD8
Dependent variable: POD 1 CD8/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	4604.85	1	4604.85	.203	.69	.092
Error	45471.40	2	22735.70			
Corrected total	53334.80	4				

Table 18. ANCOVA for CD8
Dependent variable: POD 4 CD8/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
baseline CD8	53150.84	1	53150.84	**20.17**	**.02**	**.871**
group	2222.53	1	2222.53	.844	.42	.219
Error	7904.49	3	2634.83			
Corrected total	62466.00	5				

Table 19. ANCOVA for CD8
Dependent variable: POD 8 CD8/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	3179.88	1	3179.88	.042	.85	.014
Error	226498.94	3	75499.64			
Corrected total	419884.00	5				

Table 20. ANCOVA for CD4/CD8
Dependent variable: POD 1 CD4/CD8

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	.098	1	.098	.103	.77	.049
Error	1.898	2	.949			
Corrected total	1.997	4				

Table 21. ANCOVA for CD4/ CD8
Dependent variable: POD 4 CD4/ CD8

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
baseline CD4:CD8	4.660	1	4.660	**39.47**	**.008**	**.929**
group	.038	1	.038	.318	.61	.096
Error	.354	3	.118			
Corrected total	6.484	5				

Table 22. ANCOVA for CD4/ CD8
Dependent variable: POD 8 CD4/CD8

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
baseline CD4:CD8	2.851	1	2.851	**23.4**	**.017**	**.886**
group	.000	1	.000	.002	.96	.001
Error	.365	3	.122			
Corrected total	3.857	5				

Table 23. ANCOVA for CD19
Dependent variable: POD 1 CD19/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	18871.60	1	18871.60	.486	.55	.196
Error	77657.33	2	38828.66			
Corrected total	98442.80	4				

Table 24. ANCOVA for CD19
Dependent variable: POD 4 CD19/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	1506.07	1	1506.07	.376	.58	.111
Error	12031.47	3	4010.49			
Corrected total	19689.50	5				

Table 25. ANCOVA for CD19
Dependent variable: POD 8 CD19/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	1216.02	1	1216.02	5.22	.10	.635
Error	698.77	3	232.92			
Corrected total	11670.00	5				

Table 26. ANCOVA for CD56
Dependent variable: POD 1 CD56/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
baseline CD56	2312.23	1	2312.23	**220.93**	**.004**	**.99**
group	513.34	1	513.34	**49.05**	**.020**	**.96**
Error	20.93	2	10.46			
Corrected total	3653.20	5				

Table 27. ANCOVA for CD56
Dependent variable: POD 4 CD56/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
group	13.50	1	13.50	.004	.95	.001
Error	10807.57	3	3602.52			
Corrected total	14346.00	5				

Table 28. ANCOVA for CD56
Dependent variable: POD 8 CD56/cmm

Source	Sums of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
baseline CD56	60397.60	1	60397.60	**22.81**	**.017**	**.884**
group	5876.09	1	5876.09	2.22	.23	.425
Error	7941.72	3	2647.24			
Corrected total	71940.83	5				

C-Reactive Protein (CRP). This marker of inflammation is considered to be a positive acute phase reactant meaning it increases by at least 25%

during inflammatory states. It was measured at the same intervals as the negative acute phase reactants, albumin and prealbumin, as well as the lymphocyte and lymphocyte subset counts. Mean CRP at baseline for the experimental group was 6.87 mg/dL $\pm$ SD 4.16 and for the control group it was 13.78 mg/dL $\pm$ SD 9.75 (nl CRP <0.2 mg/dL MAMC lab). The difference is significant beyond the .05 level: $t = -3.78$, $df = 4$, $p = .019$. The 95% confidence interval between means (-56.67, -8.68) excludes zero. An analysis of covariance (ANCOVA) was the recommended statistical test using baseline CRP as the covariate. First, it was important to determine a correlation between the covariate and the subsequent measures of the variable. Indeed the Pearson's correlation between baseline CRP and POD 1, POD 4, and POD 8 was high (.57) on POD 1 and yielded a perfect correlation (1.00) on POD 4 and POD 8 with significance at the .01 level. A very low correlation existed between baseline CRP and day of surgery ($r = .128$) and this was not significant so this interval was excluded from the analysis.

Next, the ANCOVA test was conducted which revealed no statistically significant differences in CRP between groups across measurement intervals. This was partly due to missing data points for some of the intervals. However, as with the other inflammatory markers measured in this protocol, the trends for both groups were as expected with a dramatic rise in CRP on the day of surgery and sustained elevation until POD 8 when levels began to decrease toward the baseline measurement (see Table 29.).

Table 29. Mean CRP ± SD for 5 measurement intervals

Group	Baseline CRP	DOS CRP	POD1 CRP	POD 4 CRP	POD 8 CRP
Experimental	6.87 ± 8.33	39.4 ± 56.8	43.4 ± 41.0	72.4 ± 62.7	35.4 ± 31.1
Control	39.5 ± 13.78	32.8 ± 41.6	169.5 ± 49.4	112.3 ± 20.8	63.1 ± 10.4

Summary of Results Addressing Specific Aim #3.

The delayed-type hypersensitivity skin test was not a useful marker of immune status or nutritional status in this small sample. The problems encountered trying to arrange this test in the facility Immunization Clinic and have the response read within 48 hours proved to be very challenging. Alternative strategies were attempted and simply did not work. The test remains important in our toolkit of physiologic immune markers but seems best suited for an inpatient population. From a feasibility standpoint this immune marker was difficult to measure and subsequently led to an insufficient amount of data with which to fully test the hypothesis. A future study would have to be designed with adequate support to do field readings. While Pearson correlations between baseline lymphocyte subset counts and subsequent measurements on DOS, POD 1, POD 4, and POD 8 yielded high values indicating a potential association between the variables, scatterplots were not as impressive. Data are presented for both groups combined and reveal a linear relationship for baseline counts of the subsets and their respective subsequent measurements for CD3 on DOS, POD 1 and POD 4; CD4 on all measurements except POD 8; CD8 on all measurements except

POD 1; CD4:8 ratio on all measurements except POD 1; and CD56 on all measurements. A sampling of scatterplots is provided in Figures 5-8.

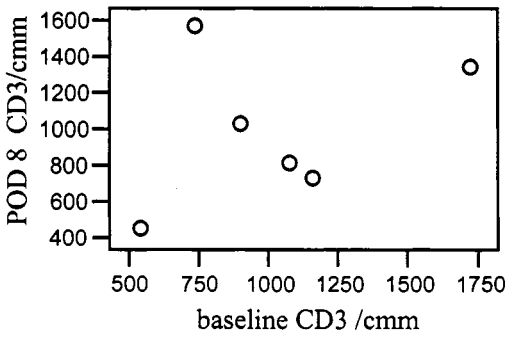

Figure 5. CD3 Correlation on POD 8

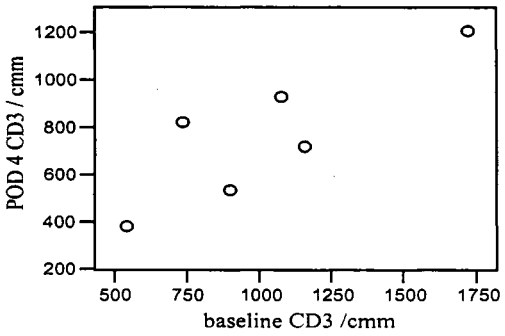

Figure 6. CD3 Correlation on POD 4

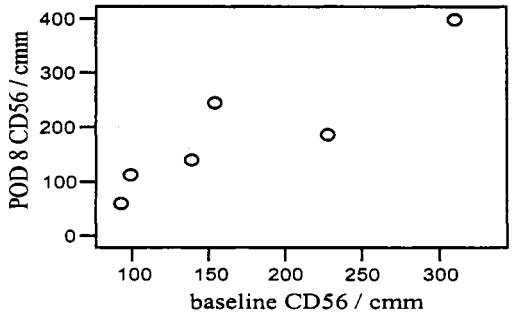

Figure 7. CD56 Correlation on POD 8

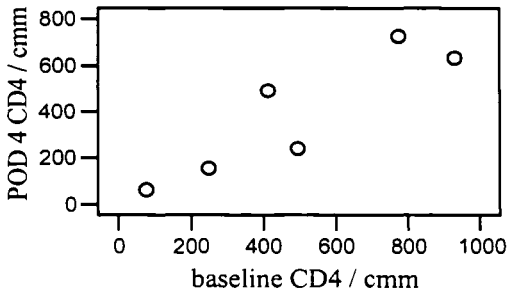

Figure 8. CD4 Correlation on POD 4

While there is no discernible effect of the nutritional intervention on this panel of lymphocyte subsets for either group, even by POD 8, it was encouraging to see that the Test of Homogeneity of Variances was upheld at all measurement intervals except on POD 4 for CD4 and CD56. This means that the randomization was effective and groups had similar variance across measures. The only measure that appears to have demonstrated a statistically significant effect from the treatment after removing the effect of the covariate was the CD56 count on POD 1. It is unclear what the clinical significance of this might be. However it does indicate that the mean CD56 count in the experimental group experienced a similar depression following the surgical insult as the CD56 count in the control group but recovered more quickly on POD 1 than the CD56 count in the control group as seen in Table 30. The rebound continued over time to POD 4. By POD 8 both counts demonstrated a positive trend toward pre-intervention levels.

Table 30. CD56 measurements

Subset classification	Baseline	Day of Surgery	POD 1*	POD 4	POD 8
CD56 Experimental	225.5 cmm	99.5 cmm	119.6 cmm	138.5 cmm	173.25 cmm
CD56 Control	154.2 cmm	110.0 cmm	86.5 cmm	86.6 cmm	165.33 cmm

* p= 0.02

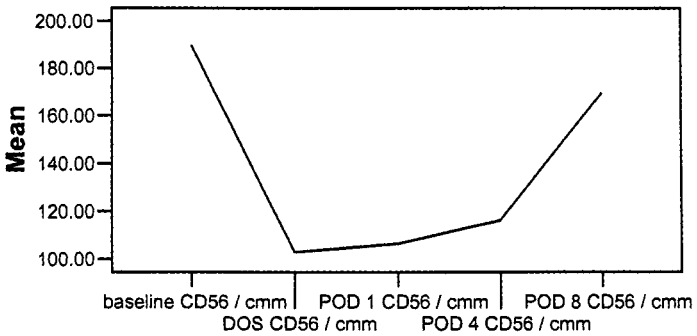

Figure 9. Mean CD56 count

Specific aim #4. To compare the difference in surgical wound healing measured by visual inspection between undernourished adult patients randomized to receive either IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

ASEPSIS Score.

Surgical wound healing was assessed using the ASEPSIS scoring method which was performed by the investigator in conjunction with the Surgeon or the Otolaryngology Chief Resident. If a measurement interval was missing post- operatively after discharge, the investigator consulted the chief resident and reviewed the chart for a description of the wound written on the

postoperative visit to the clinic. Scores were assigned each day the patient was hospitalized and on 2 follow up visits, usually one week apart. Group descriptives are provided in Table 31.

Table 31. Group descriptives

Interval	randomly assigned group	N	Mean	Std. Deviation	Std. Error Mean
asepsis score POD 1	Experimental	7	3.57	2.299	.868
	Control	5	4.80	2.387	1.067
asepsis score POD 2	Experimental	7	3.00	2.380	.899
	Control	4	5.50	1.732	.866
asepsis score POD 3	Experimental	7	2.14	1.951	.737
	Control	4	5.00	2.000	1.000
asepsis score POD 4	Experimental	7	3.00	3.559	1.345
	Control	4	4.75	1.500	.750
asepsis score POD 5	Experimental	6	.67	.816	.333
	Control	4	4.50	1.290	.645
asepsis score POD 6	Experimental	6	.67	.816	.333
	Control	4	2.50	.577	.288
asepsis score POD 7	Experimental	6	.50	.547	.223
	Control	4	2.50	.577	.288
wound score follow up wk 2	Experimental	7	.43	1.133	.428
	Control	4	5.50	7.047	3.523
wound score follow up wk 3	Experimental	7	.43	1.133	.428
	Control	4	2.50	2.645	1.322

After examining mean scores an independent t-test was performed to see if there were significant differences between the groups for wound healing on any of the measurement intervals. There were significant group differences in ASEPSIS score on POD 3, $t = -2.316$, $df = 9$, $p = .046$, on POD 5, $t = -5.819$, $df = 8$, $p < 0.001$, on POD 6, $t = -3.859$, $df = 8$, $p = .005$, and POD 7, $t = -5.543$, $df = 8$, $p = .001$. This was an unexpected finding but it is important to point out that satisfactory healing scores are within the range of 0-10.

Therefore, all wounds healed in a satisfactory manner by week three but wounds in the experimental group appear to have had shorter episodes of serous drainage or erythema.

Data on hospital length of stay (HLOS) was collected and examined as this is commonly reported in studies involving IMN. While not statistically significant, length of stay data showed the experimental group had a mean HLOS of 6.4 days (SD $\pm$ 3.1) and the control group had a mean HLOS of 11.6 days (SD $\pm$ 7.1) which is clinically significant. Complications of postoperative feeding most likely contributed to the length of stay issue.

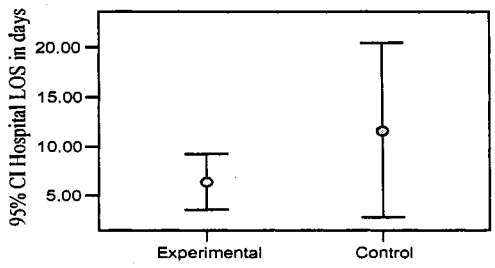

Figure 10. Mean hospital LOS - both groups

Summary of Results Addressing Specific Aim #4.

In general, almost all modified neck dissection and radical neck dissection wounds healed without infectious complications. Occasionally a patient's wound was limited to inside the oral cavity making assessments more difficult. Scores were generally low indicated satisfactory healing. Standard care was for surgical HNCA patients to receive Clindamycin® antibiotic postoperatively for 7– 10 days. Patients received points only if an additional

antibiotic was added to this standard treatment regimen. Wound photographs were taken as often as possible when assessing the wound in case the surgeon or chief resident had not seen the wound on a particular day. Agreement was 98% in wound assessments.

Chapter Five Discussion

Introduction

This pilot study investigated the feasibility of providing perioperative immunonutrition to adults who were diagnosed with head and neck cancer. Twelve individuals with different stages of the disease and varying levels of nutritional status participated in the study. The following issues were addressed: recruitment and retention of participants, intervention delivery, measurement suitability, and measurement burden. The intervention effects were determined by nutritional parameters, immunologic parameters, and wound healing outcome and will be described after discussion of feasibility aspects associated with specific aims 2, 3, and 4. Discussion of the findings is organized according to the specific aims of the study. Study limitations and strengths are discussed. Finally, implications for clinical practice are reviewed and future research directions are suggested.

Specific aim #1. To evaluate the feasibility of providing perioperative nutritional support to a convenience sample of undernourished adults undergoing surgery for head and neck cancer.

Recruitment and retention.

Although it was anticipated that 12 subjects could easily be recruited and enrolled within 12 months, actual recruitment had to be extended by 4 months. There was no need to revise eligibility requirements as almost all

patients with tumors who presented to the Otolaryngology, Head and Neck Clinic were referred to the investigator as long as their tumor was surgically resectable. The inclusion criteria were purposely broad to allow individuals with tumors of different stages and classification to participate. There was no reason to exclude HNCA patients unless they were significantly immuno-compromised upon entry into the study from recent radiation therapy, chemotherapy, chronic steroid use or other immunosuppressive drugs, or underlying automimmune disease. The decision to exclude these individuals was based on the likelihood that they would have increased operative morbidity and the potential for wound healing complications. In a future study it might be wise to exclude diabetics due to their increased risk for complications from defective inflammatory and proliferative phases of wound healing (Hotter, 1990; Orgill & Demling, 1988). While most participants were experiencing their first cancer diagnosis it was interesting to note that 4 participants had previously dealt with a cancer diagnosis; three had a previous HNCA, for one this was a recurrence of the original primary tumor, for two it was a new oral tumor site, and the fourth patient had just fully recovered from prostate cancer in the last year. Patients with head and neck cancer run a substantial risk of a second primary tumor. Such factors as smoking and alcohol intake have a carcinogenic effect on the upper airway and oral cavity and the potential for development of new tumors persists even after the patient stops smoking and drinking alcohol (Shaha et al., 2001). The majority of

patients in this study admitted to a history of alcohol and tobacco use but denied current usage once they received their diagnosis.

While almost all individuals who were approached enrolled in the study, any future studies would have to expand recruitment to more referral centers in order to obtain a sample population large enough to adequately test a hypothesis. One option might be to use a nearby VA Hospital where participants of similar age and background could be identified. However, if a more heterogeneous population was desired then participants could be recruited from the Head and Neck Service at one of the area's academic medical centers. This option would most likely add women to the sample which would offer the potential for a subgroup analysis based on gender. While there has been an in increase in the number of women diagnosed with HNCA in the United States in the last decade, large numbers are seldom seen in trials involving patients with HNCA.

Retention of study participants was very good. Of the three patients who did not complete the protocol only one chose not to adhere to the protocol regarding formula consumption. Study procedures were well-accepted by participants with very few complaints about the intervention or the laboratory tests. Coordinating laboratory tests, specialty consults, and preoperative evaluations to occur on the same day as often as possible was greatly appreciated by the patients and certainly enhanced adherence to the baseline procedure protocol. When the patient was asked to return for some aspect of

the study, like reading of the anergy panel by the Immunization Clinic, this was most often the time when data were missing. Having a research assistant trained to go to the home to obtain blood tests and administer the DTH skin test would be recommended in any future study. Also, ensuring that the daily phone calls to the patient are made and that diaries are collected would be beneficial to assessing patient adherence during the study. It was not possible to conduct the study as a double-blinded trial because it became necessary for the investigator to interact with participants on a regular basis due to the limited availability of a part-time research assistant. The investigator was able to have repeated contact with the patient and their family members and this contributed to a comfortable, trusting relationship. In a future study if products could be masked then blinding of the investigator and the patient could be easily achieved and the investigator could work closely with the patient and their family without concern for maintaining the blinded aspects of the study. It would be important to provide the same level of interaction and assistance to all patients as investigator involvement is interventional itself.

Intervention delivery.

Patients were quite honest about the amount of nutritional formula consumed during the week before surgery. However, several diaries were never returned so amounts of other food items and beverages that may have been consumed as well were not available for assessment of caloric intake or macronutrient content (fat, carbohydrate, or protein). Insufficient emphasis was

placed on this aspect of the protocol and the need for this data to help interpret findings. Having participants complete the preoperative phase at home was practical and successful. Elective surgery patients are admitted to the hospital on the day of surgery in most cases. Any preoperative intervention that occurs several times a day must happen in the home. If family members have been involved in the dialogue about the study their support can be instrumental to the success of the intervention by preparing the supplement and reminding the patient to take it.

This was the first study for the Otolaryngology, Head and Neck Service that involved a preoperative intervention. Augmenting nutritional status preoperatively was viewed as a simple and potentially effective approach to minimizing the inflammatory response after surgery while maximizing wound healing outcomes. Postoperative nutrition support is always provided to head and neck cancer patients in this facility, although preoperative support has seldom received the same attention. A group of Italian scientists studying IMN stated that postoperative enteral nutrition with a standard diet can now be considered the reference treatment (Braga et al., 2002). This statement and the fact that perioperative support seems to have the most favorable results with infectious complications was the basis of the decision to provide an intervention to all patients participating in this study. When preoperative, postoperative, and perioperative IMN support are compared, the best results

have repeatedly been found with perioperative IMN (Braga et al., 1999; Moskovitz & Kim, 2004).

Measurement suitability and burden.

The Otolaryngology, Head and Neck team comprised of one surgeon, one Chief Resident, and 4 Interns and Residents were very supportive of the study and extremely understanding of any special requests made by the investigator. Two of the Residents requested to be officially recognized as part of the study team. Due to technological barriers in the facility it was not possible to have an "order set" for all study procedures that could simply be entered into the electronic chart for study patients. Instead, the Residents had to remember to order labs, nutrition formula, DTH skin tests, and consults by the dietitian and speech pathology individually as needed. This was one reason why several lab tests were missing at different intervals for different patients. Pocket-size bright green cards with the study procedures, labs, and consults listed on them were laminated and provided to all physicians. This was not a sufficient reminder in all cases. As the study progressed there was improvement in ordering the necessary treatments and procedures at the designated intervals. In a larger study involving more than one site more attention would need to be focused on training the associate investigators. In addition, it would save much time and effort if clinic or bedside technology could be programmed to create order sets for study procedures.

Specific Aim #2: To compare the difference in the nutritional parameters between adults receiving IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

Performance of nutritional parameters.

The measurement methods used to examine nutritional parameters are highly regarded as excellent discriminators of nutritional status, including identifying malnutrition and nutritional risk. While some critics have discouraged the use of serum albumin as a sensitive measure of nutritional status many others have reported its value as a strong predictor of mortality and morbidity (Gibbs et al., 1999). Using a large national sample of Veterans Administration patients to determine the association between preoperative serum albumin and 30-day postoperative mortality and morbidity, Gibbs and colleagues (1999) concluded that for all major operations combined and for selected surgical subspecialties serum albumin level was a strong predictor of mortality and morbidity (Gibbs et al., 1999). Prealbumin was also a good choice because it performed well as a negative acute phase reactant and then reflected mild repletion as appropriate by POD 8 in this pilot study. These biochemical tests were inexpensive and easy to obtain. The choice of nutritional outcome measures has been validated in other studies. Marin and colleagues (2002) say among the variables that can be used to identify patients with nutritional deficiencies the combination of anthropometric, biochemical,

and immunological indicators is best. They used lymphocyte count, albumin, and prealbumin as indicators of nutritional deficiencies preoperatively. In their work they found that a lymphocyte count less than 1500 mm^3 was associated with a three times higher frequency of healing complications (Marin, Salido, Lopez & Silva, 2002).

Performance of Patient-Generated Subjective Global Assessment.

The Patient-Generated Subjective Global Assessment tool proved to be very useful in this sample. Patients could easily provide the necessary information and the tool was used during the consult with the dietitian early in the preoperative phase. The dietitians were also involved in the patients' care following surgery but it became obvious that they would be needed most after radiation or chemotherapy began. Many patients underwent placement of a percutaneous endoscopic gastrostomy (PEG) tube prior to starting radiation and/or chemotherapy because the toxic effects are known to result in mucositis and anorexia that severely limits intake. An observation made by the investigator was that patients who were offered the PEG tube before surgery willingly accepted it and these patients had fewer mechanical problems such as clogging and displacement postoperatively than patients fed via Dobbhoff tube. A functional feeding tube was key to the patient's timely discharge in some cases and selection of the best feeding device early on could shorten the patient's length of stay. Artificial feeding complications, swallowing dysfunction, and pain were the issues of greatest concern as patients were

discharged. These important issues required a great deal of time by all study team members and follow up appointments often focused on them as well as the long-term plan of care. These issues were present to some degree in all patients and a future study could easily incorporate quality of life measurement tools to fully capture the scope of these problems. When asked informally, patients indicated that a quality of life questionnaire would be a good idea as it would focus the physician's attention on issues of concern to the patient. Because the course of treatment is so prolonged for the patient with HNCA it seemed as if this study ended prematurely. A future study should follow the patients through the 3 or more months of radiation therapy with continued nutrition support and counseling with the goal of determining treatment options that optimize long-term outcomes such as weight maintenance or gain, improvements in swallowing/eating, decreased anxiety over the treatments, reduced pain and increased functional status, as well as improved quality of life.

Specific aim #3. To compare the difference in immune response measured by delayed-type hypersensitivity skin testing, total lymphocyte counts, lymphocyte subset counts, and c-reactive protein between undernourished adult patients randomized to receive either IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

Performance of immunologic measures.

Measurement of immunologic outcomes was satisfactory. C-reactive protein (CRP) and total lymphocyte count were sensitive measures that performed in a predictable manner. Elevation of CRP at baseline was an unexpected finding and requires further exploration. Missing values occurred when physicians neglected to order the lab tests. Serum measures were generally easy to obtain but processing of specimens was not as efficient as expected. Processing only occurred on weekdays for lymphocyte subsets. Had it been known that the lymphocyte subsets were not going to be processed on the weekend, the investigator could have had someone obtain the blood samples and freeze them until the specimen could be analyzed on the next weekday. These tests are regarded as excellent measures of an immune system response to a challenge. However, Gleeson (2005) points out that in-vitro markers are considered to be of low or medium suitability as markers of immune function. This is based largely on the lack of clear association between a change in an in-vitro immune marker and a change in susceptibility to infection. Yet, some immune markers are sufficiently reliable, sensitive, and feasible to support their measurement in human intervention studies, especially when combinations of tests representing several components of the immune response are used. In one paper measurement of circulating lymphocyte subsets was considered to be of low suitability with regard to its relevance as an immune marker that might be sensitive to dietary intervention. However, it

was strongly recommended that differential counts and identification of subsets be routinely performed in any intervention study in order to obtain valuable information about the circulation immune cell status of the individuals being studied (Gleeson, 2005).

Reading of the DTH skin test only occurred on weekdays and there were limitations associated with the process. A solution was created for this problem; the research assistant was trained to read the DTH skin test and did this at the patient's home on more than one occasion. The delayed-type hypersensitivity response has been recently recommended as one of the most suitable markers of measuring an integrated in-vivo dell-mediated response to an immune challenge (Gleeson, 2005). It is considered to be biologically relevant, with an identified association to a clinical endpoint (robust host defense against pathogens), and with lower expression in individuals who are more susceptible to infections. However, the DTH responses rely on the uncontrolled history of exposure to the antigen and have an inherently large inter-individual variation which is not well suited to comparison of immune responsiveness of small groups based on a single application. It is recommended that changes within individuals be assessed by comparing multiple DTH tests within an individual (Gleeson, 2005). Their highly regarded value in representing a person's cell-mediated immunity status is also diminished by the burden to the patient in terms of return clinic visits and long

waiting periods. A fully staffed study team would improve the success of obtaining all of the immunologic tests.

Specific aim #4. To compare the difference in surgical wound healing measured by visual inspection between undernourished adult patients randomized to receive either IMN support or standard nutrition support administered before and after surgery for head and neck cancer.

Performance of ASEPSIS tool.

Measurement of wound healing was easily accomplished with the tools selected for this process. The ASEPSIS scoring tool has been used in different surgical populations but it did not seem as useful in this sample where wound complications were less related to separation of deep tissues and more related to skin flap failure or fistula formation. Using this tool most patients remained within the level for satisfactory healing (score ≤ 10) throughout the postoperative period. This would suggest a need for development of a sensitive noninvasive method to detect small changes in healing, similar to laser Doppler or skin temperature imaging for flap assessment. Surgical intervention for HNCA frequently requires modified neck dissection or radical neck dissection with up to 3 drains inserted until POD 3 or POD 4. Having the Jackson-Pratt (JP) drains present made it difficult to estimate the proportion of the wound affected by serous discharge. The investigator discussed this with the chief resident and points were assigned in the same manner each time a JP

drain was present. For a future study a tool more specific to surgical wounds of this nature would be advantageous.

Intervention Effects

Analyses of intervention effects were done for exploratory purposes only since the small number of participants provided minimal power to detect intervention effects or differences in effects between groups. The research design also limits any ability to infer causality. This sample of patients with squamous cell carcinoma of the head and neck was a fairly homogeneous sample although tumor classification was different in almost every patient. This meant the patients were at various stages of metabolic and inflammatory insults to their body. Although not statistically proven their baseline nutritional status appeared to influence their surgical course and postoperative outcome. In this pilot study, as expected, very few statistically significant differences in clinical outcome were observed between the IMN and control groups using intention-to-treat analyses. Some of the patients did not receive the nutritional intervention preoperatively at all (n=1) and some received only a few "doses" (n=2), which would be considered less than the minimal nutritional supplement needed to benefit postoperative outcomes. While no exact amount of IMN has been determined in randomized controlled trials of surgical and critically ill patients, most investigators in this field are convinced that a minimum of 1000 mL/day is necessary to augment the immune response following the insult of surgery. All patients in this study had a minimum of 960 mL of either the IMN

or standard nutrition prescribed each day pre- and post-operatively and most had 1200 mL per day prescribed. Overall, the majority of patients consumed greater than 75% of their prescribed supplement preoperatively and postoperatively. It can be concluded that the lack of differences between groups was not due to a lack of consumption of the supplement but more likely due to the small sample size. Even larger well-conducted trials in cancer and critically ill patients have failed to show an effect of IMN on clinical outcomes (Atkinson, Sieffert & Bihari, 1998; Bower, Cerra & Bershadsky, 1995). Studies that have shown a beneficial effect of IMN on infectious complications have provided the nutritional supplementation before and after surgery, similar to the design of this study (Braga et al., 1999; FSSPEN, 1996).

The negative impact of malnutrition on the body's ability to mount an effective immune response was first recognized in the nineteenth century (Grimm & Kraus, 2001). This current pilot study in a small sample of head and neck cancer patients was conducted in order to test feasibility of delivering a nutritional intervention believed to have the potential to reverse the biological impact of malnutrition and its negative effect on immune response following surgery. The sample used for this study was not as nutritionally compromised as expected. About one-third of patients experienced weight loss >10% in the previous 6 months. What has been known for over a decade is that enterally-delivered immune-modulating nutrition either preoperatively or postoperatively can reduce postoperative infections and wound complications

in surgical patients regardless of their nutritional status (Bertrand, Piquet, Bordier, Monnier & Roulet, 2002; Braga et al., 1999). The surgical populations studied to date include gastric and colorectal cancer patients, head and neck cancer patients, cardiac, and trauma patients. Immune-modulating nutrition provided both preoperatively and postoperatively appears to offer the best approach to minimizing morbidity in cancer patients (Braga et al., 2002). Because of the high rate of reported postoperative complications in the head and neck cancer population, it was felt that an opportunity to support a positive surgical outcome, such as satisfactory wound healing, would be beneficial to these patients.

Immunologic parameters were selected after reviewing research studies that sought to measure immune responses to surgical stress (Moore, Moore, Kudsk, Brown, Bower, Koruda, et al., 1994; Ordemann et al., 2001). Similar to this pilot study, a report by Ordemann and colleagues (2001) stated that there were no differences found in the subpopulations of lymphocytes CD4, CD8, and CD4:CD8 ratio following surgery for colorectal cancer in groups randomized to undergo laparoscopic or conventional surgical resection. An earlier multicenter prospective controlled trial conducted by Moore et al. (1994) evaluated 98 patients with torso trauma who were randomized to receive either IMN or a standard stress formula. Patients receiving the IMN experienced significantly greater increases in total lymphocyte ($p=0.014$), T lymphocyte (CD3) ($p = 0.04$), and T-helper (CD4) ($p = 0.004$) cell numbers.

One additional study incorporating these immune parameters was most similar to this pilot study (Riso et al., 2000). Forty-four patients were randomized into 2 groups with one group (n=23) receiving an IMN formula and the second group (n=21) receiving an isocaloric, isonitrogenous control diet. Serum proteins, albumin and prealbumin, and immunological parameters (total lymphocytes, CD3, CD4, CD8, and CD4:CD8 ratio) decreased on postoperative day 1 in both groups. Only the IMN group demonstrated a significant increase ($p<0.05$) in the total number of lymphocytes, CD4, CD4:CD8 on postoperative day 4, and total number of lymphocytes, CD3, CD4, CD4:CD8 on postoperative day 8. Findings in the pilot study demonstrated similar trends on POD 4; by POD 8 subset counts increased for both groups. However, no other known study involving IMN has included natural killer cells (CD56) as an immunologic marker and the level of CD56 was significantly higher on POD 1 ($p = 0.02$) in the IMN group in the pilot study, possibly resulting from exposure to different treatments (nutritional formulas).

Limitations

The most obvious limitation of this pilot study is its small sample size. The sample was not large enough to provide statistical power to detect small or moderate intervention effects. This study was intended to examine the feasibility of providing a nutritional supplement to patients preoperatively in preparation for a big operation with the potential for wound healing and other

complications. Exploring the effects of the nutritional supplementation between patients randomized to one of two groups was only a secondary purpose. Therefore, the exploratory analyses of intervention effects should be interpreted with caution. The lack of statistically significant findings is not necessarily attributed to a lack of intervention effectiveness. A statistical power analysis should be performed to determine the optimal sample size when planning future experimental studies.

The homogeneous group of middle-aged to older men could be viewed as a limitation or a strength of a small study. While it was unintentional it was not unexpected that study patients would be predominantly male. Patients were identified from a group of military retirees and VA beneficiaries receiving care at a military medical center. They were between 46 and 73 years old having served in a predominantly male military force 10-40 years ago. One recent paper states that participants in human intervention studies should have a defined age range, since immune functions in the elderly can be decreased when compared with young individuals (Lesourd, Raynaud-Simon & Mazari, 2002). The fairly narrow age range for this population is therefore a strength regarding the selected immunologic outcomes. Also, the sex of study participants affects immune functions through endogenous estrogenic effects and exogenous hormones, therefore the all male study sample provides good data for comparisons. There have been reports of gender differences in immune responses and clinical outcome. Many large survey studies in

hospitalized patients such as trauma patients, patients with hip fractures, and surgical ICU patients that show mortality and/or infection rates are lower in women than in men. However, one large study of IMN therapy in critically ill patients performed subgroup analysis with gender and found women who received IMN had an increased rate of infectious complications (53.3% vs 35.8%, $p = 0.029$) compared to the control group (Kieft, Roos, van Drunen, Bindels, Bindels & Hofman, 2005). Hospital length of stay was also longer compared to the control group, Kaplan-Meier median 42.0 vs 26.0 days, $p = 0.021$. The mechanism for this effect in women is unclear but investigators hypothesized that arginine content in the IMN may have led to increased growth hormone secretion. While a gender analysis could not be performed with this data set it would be of great interest in a larger, more diverse population.

Another limitation is related to the amount of missing data. The burden of preoperative consultations and baseline laboratory tests proved too difficult for most patients to accomplish independently. These activities went more smoothly when the investigator could coordinate the appointments so it was convenient for the patient to return on one additional day or if the investigator could escort the patient through the system of appointments and laboratory tests. The protocol was written to minimize additional preoperative requirements but all patients undergo an extensive work-up prior to surgery even when they are not in a research study. Usual consultations were with

support services such as speech pathology, oral surgery, radiation oncology, anesthesiology, nutrition, and the primary care physician. Patients often needed medical clearance for surgery which involved cardiologists, endocrinologists, and urologists. Patients were often required to make multiple trips back to the hospital so those who lived long distances away often did not complete all of the workup, leaving missing data points. Long waiting times in clinics was also a deterrent, especially if patients were in pain. As previously mentioned, in a future study that involves an extensive preoperative workup it would be advantageous to hire a nurse on the study staff who would go to the patient's home and obtain laboratory tests, inject and read the DTH skin test, provide preoperative teaching, and possibly PEG tube teaching, as well as emotional support.

The ability to explore trends in the data of the intervention effects of nutritional supplementation evaluated in this study is limited by lack of data regarding preoperative diet. Because many patients did not return their diaries it is uncertain what effect any other foods and beverages in their diet may have had on their nutritional status. The amount of protein, fat, carbohydrate, vitamins, and minerals in their diet prior to surgery may have been sufficient to ensure satisfactory healing of the surgical wounds. While only one patient admitted to taking regular herbal supplements, it is unknown if other patients took vitamins or herbs that may have also contributed to their postoperative

healing. It is also possible that providing extra support and encouragement to patients before surgery gave them hope and contributed to positive outcomes.

Limitations exist to any measurement of immune status. The background diet of an individual contributes to their general nutritional status and their immune status. Diet histories were really only available for the first week of the study. Alcohol consumption and smoking both affect immune function and should be properly controlled. The individual phenotype has yet another way of determining the functional status of immune cells. It was recommended in one paper that natural killer cell activity be defined as low or high at baseline and then random allocation of individuals according to this value be performed in studies focusing on this measure of immune function in order to avoid statistically significant pre-study differences in NK cell activity. Low natural killer cell activity is correlated with increased cancer risk and with increased mortality in the elderly (Ogata, An & Shioi, 2001).

Other factors that were not controlled for in this study but have potential impact on the results of the immune markers include controlling for the circadian rhythm of immune cell activities and seasonal variation in immune functions. Timing of the blood collection and the fasting period prior to specimen collection should be standardized and seasonal variations due to environmental factors like daily light exposure, climate, exposure to antigens, and diet should be recorded as they all may affect immune function. One additional limitation to the use of biochemical markers to assess immune

function is that they were a quantification of the response to a surgical challenge but they were not a functional measure because no attempt was made to evaluate how they would react upon stimulation with an actual antigen such as pokeweed mitogen which stimulates all lymphocytes or phytohemagglutinin which stimulates T cells. Other factors recorded, but not controlled for, were current and past smoking habit and current and past alcohol use. Both alcohol and tobacco have been shown to impact morbidity and recovery after surgery. Studies have shown that individuals who abuse alcohol are subject to higher morbidity and prolonged recovery after operation than nonabusers (Tonnesen & Kehlet, 1999). Interventions that incorporated preoperative alcohol abstinence for 4 weeks reduced the increased morbidity after colonic surgery compared with patients who continued their drinking habits (Tonnesen, Rosenberg & Nielsen, 1999). Smoking contributes to surgical risk because it is associated with a marked reduction in phagocytic and microbicidal activity, possibly related to reduced proinflammatory cytokine activity (Kotani, Hashimoto & Sessler, 2000). Further studies are needed to evaluate the role of preoperative smoking cessation and abstinence from alcohol in a variety of surgical populations.

Strengths

This pilot study was a small manageable project that was able to test all aspects of the perioperative protocol as originally designed. It was the first study of its kind in the head and neck cancer population at this large military

medical center. Although statistically significant improvements in the secondary outcome variables were not common, and may have occurred by chance, when differences were found they were congruent with the theoretical hypothesis. Another possible explanation for any significant findings in immune response in this small sample could be the multiple comparisons performed at several different intervals for the different lymphocyte subsets. However, there seems to be support for the theoretical framework guiding this study and the scientific principles of immune-modulating nutrition. The trends in nutrition parameters and immune parameters were similar to several other randomized controlled trials in large populations of cancer patients (Braga et al., 2002; Braga et al., 1999; Gianotti et al., 2002).

Having the opportunity to manage 5-7 subjects on the protocol in each group provided the investigator with sufficient clinical data to examine use of the measures to operationalize immune and wound responses, and assess for trends in these responses for the three secondary aims. The twelve patients provided valuable insight into the complex care of head and neck cancer that demands the services of a multidisciplinary team of health care professionals and the complexity of executing clinical studies in this vulnerable population. The study team was interdisciplinary and included head and neck specialty physicians, speech pathologists, nurses with oncology experience, and dietitians with oncology expertise. Support services for the inpatient and postoperative phases of care came from radiation oncology, social work,

pathology, radiology, and physical therapy departments. Overall, support for the protocol was widespread with very few barriers to accomplishing the goals of the study.

An additional strength of the study is that it provides pilot data supporting feasibility and measurement suitability for future studies. The pilot data can also be used to look at historical records and compare outcomes between patients in the study and previous patients who had no formal perioperative nutrition support. This could lead to new insights about the effectiveness of the intervention. It could also generate new hypotheses to be tested in future studies.

Future Research Directions

The field of immune-modulating nutrition has continued to grow even after more than a decade of research. New applications for its use and new formulas appear in the scientific journals every month. Some scientists refer to IMN as pharmaconutrients or nutraceuticals because it behaves much like a drug in that it appears to rely on a specific amount of absorption into the tissues to be effective. With this line of thinking, research should be focusing on delineating minimum and maximum amounts of daily supplementation in order to modulate immune responses.

Immunonutrition is the supplementation of standard enteral formulations with specific nutrients that are known to favorably manipulate the biologic response to injury, inflammation, and infection (Wyncoll & Beale,

2001). Because feeding reverses malnutrition-induced immune depression, investigators have sought to identify the specific components of the diet responsible for the reversal of immune depression (Heys, Schofield & Wahle, 2004). The numerous dietary compounds that appear to influence immune function include dietary peptides, arginine, glutamine, nucleic acids, vitamin C, vitamin E, and vitamin A. Presently it is not clear whether it is the combination of immunonutrients that is crucial or if a single nutrient could prevent the immune depression that accompanies surgery and critical illness. Based on current studies in the literature, combination immunonutrition seems to be more powerful (Bower, Cerra & Bershadsky, 1995). Future studies should continue to test single nutrients in various disease states to identify those that may suppress the inflammatory response associated with surgery and/or promote wound healing.

Many advances have been made in recent years regarding surgical options for head and neck cancer. Less invasive and extensive operations can be performed with the appropriate regimen of radiation or chemoradiation therapy following surgery. However, the toxic effects of radiation and/or chemotherapy have a significant effect on the nutritional status and quality of life of patients with head and neck cancers. From this pilot study it was obvious that body weight and energy level rapidly decline with radiation and chemotherapy as nausea, vomiting, anorexia, and taste alterations become daily disruptions. Quality of life issues are also a priority for patients but they

complain that 'no one seems to notice'. Future studies should be of longer duration so as to follow these patients through the second health crisis that accompanies postoperative therapies such as radiation. In addition, the observation that patients with PEG tubes seemed to have fewer nutritional setbacks and a smoother hospital course would be worth examining more closely in another study that could randomize patients to receive this procedure preoperatively.

Lastly, further work on the genetic predisposition for head and neck cancer would be a significant contribution to the oncology literature. One patient had no history of smoking or alcohol abuse and no known exposures to toxins in the work environment. There are many scientific reports of viral etiologies for head and neck cancer, specifically human papilloma virus. Along with a closer look at the primary disease, it would be informative and relevant to development of behaviorally focused interventions for these patients, to examine the recurrence rate in patients who continue to smoke and drink alcohol compared to those who quit smoking and drinking. The recurrence rate in this small sample was 3/12 or 25% in only 16 months. Four patients were undergoing surgery for a recurrence of a previous oral cavity or laryngeal tumor. Two patients in the study succumbed to their disease within 6 months. There is important work to be done to further elucidate genetic and environmental causes of the disease and to incorporate nutritional and other biologic and behavioral therapies into the treatment of the disease. A larger,

multi-site randomized controlled trial of perioperative immune-modulating nutrition in malnourished men and women undergoing surgery and subsequent radiation therapy for HNCA would be the next step in planning future research. The trial should plan to involve different settings (non-military) in order to recruit a diverse sample that could provide insight into the disease at many different levels. Ultimately, results could transfer to other vulnerable cancer populations.

Implications for Clinical Practice

The findings of this study have useful implications for nurses in both inpatient and outpatient settings, and for all health care providers involved in the perioperative care of oncology patients, specifically those with head and neck cancer. Nutritional issues are numerous for cancer patients but this study demonstrated that a simple preoperative intervention could promote positive surgical outcomes. Nurses working in the outpatient clinics or in the pre-surgical care clinics are in the best position to make recommendations to patients as they prepare for their upcoming surgery. The recommendation from a respected health care professional that 5-10 days of nutritional supplementation (with or without immune-modulating components) and cessation of smoking and drinking will assist with postoperative healing would be well-received by most patients. The interaction with a speech pathologist and a dietitian is critical to establishing baseline swallowing and nutritional status in these patients. It is highly recommended that consultations with these

specialties be incorporated into the preoperative plan of care for all HNCA patients. Dietitians are in a position to make a strong case for placement of a PEG tube if swallowing difficulties or prolonged artificial feeding is anticipated.

All laryngectomy patients will have difficulty communicating immediately after surgery. There were limited resources for the patient to use for communication except occasionally a pad of paper and a pen. The investigator found that a small erasable white board was the perfect solution so the patient could write brief questions or comments and simply erase them. Unit funds could be used to purchase a few of these white boards so that patient's have an immediate option for communication. The Laryngectomee Support Group at the facility meets monthly and discusses pertinent postoperative issues. All laryngectomy patients should be informed about this group by the nurses and speech pathologists and encouraged to participate when possible. New laryngectomees learn from the individuals who have lived with and developed coping strategies for the many postoperative issues over the years. The social workers, chaplains, and mental health specialists may be called upon to assist with individual needs or requests. Ideally, other resources in the community or on-line will be shared with all head and neck cancer patients. Aside from the clinical care required, the nurse's main role is that of facilitator and patient advocate as the patient recovers from surgery and resumes his or her life with many new challenges. Coordinating specialty

consultations and providing education about diet/feeding tube care, wound care, secretion and airway management, activity restrictions, and pain management are critical to a smooth, uneventful recovery.

Conclusion

This pilot study "Perioperative Immunonutrition in Head and Neck Cancer" applied a proven scientific approach to modulation of the immune response to a high risk group of cancer patients. There is no dispute in the literature that head and neck cancer patients are very often malnourished at the time of diagnosis and subsequently they are more prone to infectious complications and impaired wound healing. This study also explored possible effects on nutritional status, immunologic status, and wound healing when comparing two groups of individuals randomized to receive either standard formula or immune-modulating formula. While most findings were not statistically significant, trends were noted for a faster rebound towards baseline levels for lymphocyte subsets (CD19 & CD56), and CRP in the treatment group. There could be many explanations for this but one might be that IMN does in fact lessen the inflammatory response and promote a more rapid return to baseline levels for B cells and NK cells as well as acute phase reactants. In addition, although not statistically significant, the length of stay for the treatment group was considerably less than the control group; 6.4 days versus 11.2 days. This is clinically significant with a large impact on nursing workload, resource utilization, and cost effectiveness.

The patients in this study welcomed the opportunity to participate in research while also helping themselves avoid potential complications that come with a major surgical procedure. They provided a great deal of insight into a complex, all-consuming disease process that would change their lives forever. Some changes in measurement of immune status such as omitting the DTH skin test and possibly adding cytokine parameters would strengthen the study.

This study clearly supports the need for further research efforts. As a pilot study it highlights areas of possible improvement for the preoperative phase of data collection. In order to maximize data points for all patients a research assistant should be trained to go to the home to complete blood tests, examine diary entries each day, discuss diet issues, and provide ongoing education. The idea by Philpott and Ferguson (2004) that nutrition therapies may eventually have a greater role in cancer surveillance and cancer prevention suggests there will be many opportunities for research in the future (Philpott & Ferguson, 2004). Nurses must collaborate with other disciplines as they design future clinical research studies that can address the multitude of biopsychosocial care issues for the patient with head and neck cancer.

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APPENDIX A Volunteer Agreement Affidavit

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25 or AR 40-38; the proponent agency is OTSG

PRIVACY ACT OF 1974

Authority:	10 USC 3013, 44 USC 3101 and 10 USC 1071-1087
Principle Purpose:	To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.
Routine Uses:	The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs, teaching, adjudication of claims, and for the mandatory reporting of medical condition as required by law. Information may be furnished to Federal, State and local agencies.

Disclosure: The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ SSN _____ having full capacity to consent and having attained my _____ birthday, do hereby volunteer to participate in the research protocol **Perioperative immunonutrition for head and neck cancer** under the direction of **MAJ Douglas Sorensen, M.D., MC, and Mary S. McCarthy, RN, MN,** conducted at Madigan Army Medical Center.

The implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by _____.

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. **Should any further questions arise concerning my rights on study-related injury I may contact the Center Judge Advocate at Madigan Army Medical Center, (253) 968-1525.**

I understand that I may at any time during the course of this study revoke my consent and withdraw from the study without further penalty or loss of benefits; however, I may be required (military volunteer) or requested (civilian volunteer) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

PART B - EXPLANATION OF WHAT IS TO BE DONE

INTRODUCTION: You have been asked to participate in a clinical research study conducted at Madigan Army Medical Center because you have been diagnosed with cancer of the head or neck and may benefit from specialized nutrition before surgery. Participation is entirely voluntary. You may refuse to answer questions at any time. You may refuse to participate or withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled. About fourteen (14) patients will be participating in this study over the next year.

PURPOSE: Patients with head and neck cancer are at particular risk for malnutrition before, during, and after their treatment as a result of nausea or vomiting related to chemotherapy and radiation therapy, inability to eat because of the tumor location, or loss of appetite due to substances released from the tumor, fatigue, and depression. Previous studies suggest that a good nutritional status will help you recover sooner and with fewer complications. In the past 10 years we have learned that nutrition formulas modified with special nutrients such as amino acids (protein), omega-3 fatty acids (fats), and vitamins A, C, and E can offer a significant advantage to patients undergoing major surgery by supporting the immune system. This modified nutrition is called immune-enhancing nutrition or immunonutrition. The purpose of this study is to provide immune-enhancing nutrition to patients with head or neck cancer before and after surgery so that their immune system is ready to handle the surgical procedure and protect the wound from infection. This research is new in that we will provide immune-enhancing nutrition prior to surgery when it is usually only started after surgery. Some researchers believe it takes 5-7 days before it is effective which is why we want to give it for 7 days before surgery. It is standard procedure to provide nutrition as a tube feeding for 7 days after this type of surgery. If this specialized nutrition does improve nutritional status and immune response then it

could mean your surgical wound heals faster and you may have a shorter hospital stay.

PROCEDURES: Your physician states that you have cancer of the head or neck and you may benefit from a nutritional supplement prior to surgery. This study involves randomization which means you have a 50-50 chance of receiving an immune-enhancing supplement or a standard supplement for the 7 days before surgery. If you have a feeding tube your supplement will be administered by the tube. If you do not have a feeding tube, you will drink your supplement. Supplements will be provided to you and come in juice box–type containers. All instructions will be provided by a registered nurse who knows which group you have been assigned to. Your physicians and the associate investigator (Ms. McCarthy RN) will not know your group assignment. It will be very important for you to follow the instructions for taking the supplement provided by the registered nurse. Your preoperative blood work will include specimens for this study such as baseline immune measures (white blood cells) and nutritional measures (albumin and prealbumin). The amount of blood necessary for these tests is about 1 teaspoon. This amount will be taken for the purposes of this study on five occasions. Every effort will be made to see that it is obtained when other bloodwork is being drawn. You will also have a skin test placed with a painless device on your forearm by the immunization clinic staff. Within 48 hours we will check for a response, such as a raised red area, that will help us evaluate your nutritional status prior to surgery. The test will be repeated 8 days after surgery. You will also receive a metabolic cart study which is part of our nutritional assessment used to estimate your calorie needs. This is a 15 minute test that requires you to breathe into a mask so that air coming from your lungs can be analyzed. You will be asked to answer a few short questions about your diet at the time of that test.

A research nurse will phone you every day or come to your house if necessary to answer any questions or assist with administering the supplements during the 7 days before surgery. You will be asked to keep a daily diary recording your food and supplement intake before surgery. You will also see a dietitian and speech pathologist at least 4 times during the study. They will help us track your nutritional status and your ability to resume a normal diet after surgery.

After surgery all study patients will receive tube feeding for 7 days with the same supplement as you received before surgery, either the immune-enhancing one or the standard one. This time the supplement will run continuously at a slow rate. This is recommended by previous studies that demonstrated a positive effect on wound healing and fewer complications of surgery using tube feedings after surgery. During the 7-day period after surgery you will also be seen by a wound nurse who will evaluate the healing of your

surgical wound. In order to have a record of your wound healing, photos of just the surgical wound will be taken. After 7 days you will be switched to a standard hospital formula or you may begin an oral diet. After discharge from the hospital you will have follow-up visits each week with your physician. A nurse from the research team will visit with you to check your wound and to ask about your food intake. You may also see the dietitian, the wound nurse, and the speech pathologist at these visits. The research nurse collects many other pieces of information from all study patients. This information is in your chart. Information that is collected includes your height, weight, age, medical history, vital signs, medications, and laboratory and x-ray results. Some of this information may be obtained from your hospital records after you are discharged. The research nurse will also collect information regarding any wound healing complications or other infections for a total of 30 days.

POTENTIAL BENEFITS: Previous studies using immune-enhancing nutrition for cancer patients have demonstrated fewer infections, improved nutritional status, and beneficial effects on the immune system and wound healing. However, many of the previous studies were not with head and neck cancer patients. It is felt that studies conducted with other types of cancer patients may have the same benefits for head and neck cancer patients. Immune-enhancing nutrition has the potential to change how the body responds to injury or surgery and minimize the risk of infection and malnutrition. We will pay very close attention to your physical and mental health throughout this study by using many experts from medicine, nursing, and nutrition. Findings from this study may not benefit you directly but they will most certainly be helpful in identifying whether or not nutritional support can improve the outcomes of surgery for persons with head and neck cancer.

RISKS, INCONVENIENCES, AND DISCOMFORTS: There have been no reports of discomfort from the oral nutritional supplements. Tube feedings are generally well-tolerated but some patients do complain of gastrointestinal symptoms of cramping, bloating, diarrhea, or constipation. These symptoms generally subside with slower administration of the feeding. The phone calls from the research nurse may be inconvenient but they are simply to check for any questions or concerns you may have regarding the supplement or tube management; they will be no more than 10 minutes long. The home visits before or after surgery may seem intrusive or disruptive but this is offered as a convenience for you and clinic visits can be substituted for most of the home visits at your request. All follow-up visits can coincide with physician follow-up visits to minimize any inconvenience for you.

Blood Draws: You may experience pain, bruising, bleeding or discomfort at the site where the needle enters the skin. Also, dizziness, fainting or slight infection at blood drawing site may occur in rare cases.

ALTERNATIVES TO PARTICIPATION: Alternative treatments which could be considered in your case include supplemental nutrition prescribed by your doctor that you buy at the grocery store. Your doctor or dietitian can provide detailed information about the various supplements (e.g. Gatorade, Boost, Carnation Instant Breakfast) available to you based on your current medical condition.
COMPENSATION: You will not be paid for your participation in this study.
CONFIDENTIALITY OF RECORDS: The Institutional Review Board (IRB) at Madigan, the Uniformed Services University of the Health Sciences, Bethesda, MD, the Food and Drug Administration (FDA), the University of Washington Human Subjects Division, and other governmental agencies who provide oversight for human subject protection may see your records. Otherwise, only the research team conducting this study will have access to the records from this study. All records will be kept in a confidential form. Information gained from this study may be used as part of a scientific publication, but you will in no way be personally identified. Complete confidentiality cannot be promised, particularly for military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities. Your identity (name and other identifiers) will be linked to the study data for 3 years or until results from the study have been published.
BLOOD & TISSUE SAMPLES: All blood and tissues samples will be destroyed once the study is completed and not stored for use in future research.
NEW FINDINGS: Significant findings that occur during this study that might affect your decision to participate in the study will be discussed with you. Any significant findings developed from this study will be available to you and may be obtained from your physician.
REMOVAL STATEMENT: Your participation in this study may be terminated without your consent if conditions occur which might make your continued participation dangerous or detrimental to your health; or if military contingency requires it; or if you become ineligible for military care as authorized by Army regulation.
OTHER INFORMATION: If you should require medical care for injuries or disease which result from participation in this study, the medical care to which you will be entitled is the same as that which you are already entitled as a DoD health care beneficiary. This does not include domiciliary (home care) or nursing home care. Should you require treatment for study-related injuries you should contact your surgeon in the Madigan ENT Clinic at 253-968-1430.

You are encouraged to ask any questions, at any time, that will help you to understand how this study will be performed and/or how it will affect you. **You may contact the principal investigator, Dr. Sorensen at (253) 968-1430 or Ms. McCarthy RN at (253) 968-3695.**

Funding for this study is provided by the TriService Nursing Research Program in Bethesda, MD thru a research agreement with The Geneva

Foundation.
If you have any questions or concerns about this study or your rights as a study subject you may contact the Institutional Review Board, Madigan Army Medical Center, Tacoma, WA 98431, (253) 968-0149, or the Human Subjects Division at the University of Washington at 206-543-0098.

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE AGREEING TO PARTICIPATE IN THIS STUDY.

You will be given a copy of this consent document for your records.

I do ☐ _____ do not ☐ _____ (check one & initial) consent to the inclusion of this form in my outpatient medical treatment record.

SIGNATURE OF VOLUNTEER	DATE	PRINTED NAME OF VOLUNTEER
_____	_____	_____
PERMANENT ADDRESS OF VOLUNTEER _____ _____		

Name of person administering consent: _____

Signature of person administering consent: _____Date: _____

APPENDIX B Demographic Form

SUBJECT DEMOGRAPHICS

Subject # _____

Gender 1 2

Race: ___Asian, Pacific Islander, ___Black, African-American, ___Hispanic, ___American Indian, ___White

DOB (m/d/y) ____/____/____

Admission Dx _____

Tumor classification _____

Prior radiation therapy/date Yes / No _____

Prior surgery / date Yes / No _____

Date & time enrolled in study ____/____/____

Date of PEG/Dobbhoff Placement (if applicable) ____/____/_____

Hospital Admission Date (m/d/y) ____/____/_____

Initial Home Visit Date (m/d/y) ____/____/____ Time:

Initial Height (ins) / Weight (kgs)/BMI _____/_____

Usual Body Weight _____

Ideal Body Weight _____

Admission Body Weight _____

Sorensen ENT Study '04 Form 1

APPENDIX C Patient-Generated Subjective Global Assessment (PG-SGA)

1. **Weight** (See Table 1 Worksheet)

In summary of my current and recent weight:

I currently weigh about _____ pounds

I am about ____feet _____in tall

1 month ago I weighed about _____ pounds
6 months ago I weighed about _____ pounds

During the past 2 weeks my weight has:

□ decreased (1) □ not changed (0) □ increased (0)

2. **Food Intake:** As compared to normal, I would rate my food intake during the past month as:
□ unchanged (0)
□ more than usual
□ less than usual (1)

I am now taking:
□ normal food but less than normal (1)
□ little solid food (2)
□ only liquids (3)
□ only nutritional supplements (3)
□ very little of anything (4)
□ only tube feedings or only nutrition by vein (0)

3. **Symptoms:** I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):

□ no problems eating (0)
□ no appetite, just did not feel like eating (3)
□ nausea (1) □ vomiting (3)
□ constipation (1) □ diarrhea (3)
□ mouth sores (2) □ dry mouth (1)
□ things taste funny or have no taste (1)
□ problems swallowing (2)
□ smells bother me (1)
□ pain; where? (3)_____
□ feel full quickly (1)
□ other**(1) _____

** Examples: depression, money, or dental problems

4. **Activities and Function**: Over the past month I would generally rate my activity as:

□ normal with no limitations (0)

□ not my normal self, but able to be up and about with fairly normal activities (1)

□ not feeling up to most things, but in bed or chair less than half the day (2)

□ able to do little activity and spend most of the day in bed or chair (3)

□ pretty much bedridden, rarely out of bed (3)

Additive Score of the Boxes 1-4 ☐

APPENDIX C Patient Generated Subjective Global Assessment (continued)

5. **Disease and its relation to nutritional requirements** (see Table 2)
All relevant diagnoses (specify)

_____

Primary disease stage (circle if known) I II III IV Other

_____

Age _____

6. **Metabolic Demand** (See Table 3 Worksheet) Numerical score from Table 2 ☐ B
□ no stress □ low stress □moderate stress

□ high stress Numerical score from Table 3 ☐ C

7. **Physical** (See Table 4 Worksheet) Numerical score from Table 4 ☐ D

Global Assessment (See Table 5 Worksheet)

☐ Well-nourished or anabolic (SGA-A)

☐ Moderate or suspected malnutrition (SGA-B)

☐ Severely malnourished (SGA-C)

Total numerical score of boxes
A + B + C + D =

(See triage recommendations below)

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). First line nutrition intervention includes optimal symptom management.

0 – 1 No intervention required at this time. Re-assessment on routine and regular basis during treatment.

2 – 3 Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and laboratory values as appropriate.

4 – 8 Requires intervention by dietitian in conjunction with nurse or physician as indicated by symptoms survey (Box 3).

$\geq$ 9 Indicates a critical need for improved symptom management and/or nutrient intervention options.

Clinician signature _____

Date_____

APPENDIX D Subject Preoperative Diary

Day 1

Remember, you have made a good decision to help your surgery go well.

Please drink all nutritional product prescribed for you today (see notecard).
Record any other foods or drinks you consume today on this page.
Record any discomforts, concerns, or questions you may want to talk to the nurse about when she calls. Write them on this page.
The nurse will call every day at the time you have discussed with her.
Please feel free to call Mary McCarthy RN if you have any questions (phone number on notecard).

Complaints or discomforts:

List other foods and estimate quantity eaten:

List other drinks and estimate quantity consumed:

Questions to ask the nurse:

Day 2

Every little bit helps, drink all that you can.

Please drink all nutritional product prescribed for you today (See notecard).
Record any other foods or drinks you consume today on this page.
Record any discomforts, concerns, or questions you may want to talk to the nurse about when she calls. Write them on this page.
The nurse will call every day at the time you have discussed with her.
Please feel free to call Mary McCarthy RN if you have any questions (phone number on notecard).

Complaints or discomforts:

List other foods and estimate quantity eaten:

List other drinks and estimate quantity consumed:

Questions to ask the nurse:

Day 3

Don't forget you can freeze the drink or make smoothies ☺

Please drink all nutritional product prescribed for you today (See notecard).
Record any other foods or drinks you consume today on this page.
Record any discomforts, concerns, or questions you may want to talk to the nurse about when she calls. Write them on this page.
The nurse will call every day at the time you have discussed with her.
Please feel free to call Mary McCarthy RN if you have any questions (phone number on notecard).

Complaints or discomforts:

List other foods and estimate quantity eaten:

List other drinks and estimate quantity consumed:

Questions to ask the nurse:

Day 4

Keep up the good work, you are half way done!

Please drink all nutritional product prescribed for you today (see notecard).
Record any other foods or drinks you consume today on this page.
Record any discomforts, concerns, or questions you may want to talk to the nurse about when she calls. Write them on this page.
The nurse will call every day at the time you have discussed with her.
Please feel free to call Mary McCarthy RN if you have any questions (phone number on notecard).

Complaints or discomforts:

List other foods and estimate quantity eaten:

List other drinks and estimate quantity consumed:

Questions to ask the nurse:

Day 5

Congratulations! You are more than half way done!

Please drink all nutritional product prescribed for you today (see notecard).
Record any other foods or drinks you consume today on this page.
Record any discomforts, concerns, or questions you may want to talk to the nurse about when she calls. Write them on this page.
The nurse will call every day at the time you have discussed with her.
Please feel free to call Mary McCarthy RN if you have any questions (phone number on notecard).

Complaints or discomforts:

List other foods and estimate quantity eaten:

List other drinks and estimate quantity consumed:

Questions to ask the nurse:

Day 6

You are doing great, only one more day!

Please drink all nutritional product prescribed for you today (see notecard).
Record any other foods or drinks you consume today on this page.
Record any discomforts, concerns, or questions you may want to talk to the nurse about when she calls. Write them on this page.
The nurse will call every day at the time you have discussed with her.
Please feel free to call Mary McCarthy RN if you have any questions (phone number on notecard).

Complaints or discomforts:

List other foods and estimate quantity eaten:

List other drinks and estimate quantity consumed:

Questions to ask the nurse:

Day 7

Hooray! This is your last day to drink the formula!

Please drink all nutritional product prescribed for you today (see notecard).
Record any other foods or drinks you consume today on this page.
Record any discomforts, concerns, or questions you may want to talk to the nurse about when she calls. Write them on this page.
The nurse will call every day at the time you have discussed with her.
Please feel free to call Mary McCarthy RN if you have any questions (phone number on notecard).

**Your surgery is tomorrow so remember the anesthetist's instructions.
One of the research nurses will look in on you after surgery.

Complaints or discomforts:

List other foods and estimate quantity eaten:

List other drinks and estimate quantity consumed:

Questions to ask the nurse:

APPENDIX E ASEPSIS Tool

Subject ID# _____

WOUND FACTORS AND APPRAISAL

TOTAL SCORE: Indicates Category of Infection	POINT SCALE FOR THE DAILY WOUND INSPECTION

		Proportion of Wound Affected (%)					
0-10 Satisfactory Healing	**Wound Characteristic**	0	<20	20-39	40-59	60-79	>80
11-20 Disturbance of Healing	Serous Exudate	0	1	2	3	4	5
21-30 Minor Wound Infection	Erythema	0	1	2	3	4	5
31-40 Moderate Wound Infection	Purulent Exudate	0	2	4	6	8	10
>40 Severe Wound Infection	Separation of Deep Tissue	0	2	4	6	8	10

A	Additional Rx	Antibiotic(s) 10	Drng Local Anesth 5	Debride Gen Anesth 10
S	Serous Discharge	Daily 0-5		
E	Erythema	Daily 0-5		
P	Purulent Exudate	Daily 0-5		
S	Separation of Deep Tissue	Daily 0-5		
I	Isolation of Bacteria	10		
S	Inpatient Stay > 14 Days	5		

ASEPSIS RATING: SURGICAL WOUND

	CRITERION	POD1	POD2	POD3	POD4	POD5	POD6	POD7	WK2	WK3
A	Additional Rx: Antibiotic(s)									
	Drainage of pus under local anesthesia									
	Debride wound under general anesthesia									
S	Serous Discharge									
E	Erythema									
P	Purulent Exudate									
S	Separation of Deep Tissue									
I	Isolation of Bacteria									
S	Inpatient Stay > 14 Days									
	TOTAL SCORE									

APPENDIX F Daily Nutritional Intake Form

Subject Number:_____
Subject's Initials:____ ____

DAILY DATA COLLECTION (Nutritional Intake)

Study Day	1	2	3	4	5	6	7
Date (m/d/y)							
Weight (kgs)							
Formula/Volume Study Feed Prescribed (ml/24hr)							
Volume Study Feed Received (ml/24 hr)							
Calories (kcal/24hr) from Study Feed + Other							
Protein (g/24hr) from Study Feed + Other							
Location of Feeding Tube as confirmed by clinician							
**Diarrhea *f*(0,1,2,3)							
***Constipation *f*(0,1,2,3)							
Vomiting *f*(0,1,2,3)							
Gas *f*(0,1,2,3)							
Abdominal distention *f*(0,1,2,3)							
Witnessed aspiration (x,y)							
Feedings decreased,interrupted or discontinued, how long? (list all that apply: see taxonomy)							

*Study Day 1 begins with the start of the nursing shift on the day on which study feeds were initiated.
**Three or more WATERY bowel movements per day, or ≥ 500 mL/day LIQUID stool x 2d
***Three days or more without a bowel movement

f 0 = none
extubation)
1 = mild, usually transient and easily tolerated, special action optional
2 = moderate, special action is needed
3 = severe, discontinuation of product is required and/or situation is life-threatening

"Interruption" Taxonomy
a. hi gastric residuals
b. Procedure radiology, surgery,
c. NG tube dysfunction
d. vomiting
e. abdominal distention
f. other, specify

x: documented in medical record, y: nurse/MD/SLP verbal confirmation

VITA

Mary S. McCarthy

CURRENT POSITION

Nursing Research Service
Nurse Researcher GS-13
Madigan Army Medical Center
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EDUCATION

2006	School of Nursing, University of Washington Seattle, WA	PhD
1989	School of Nursing, University of Washington Seattle, WA	MN
1980	D'Youville College Buffalo, NY	BSN

SPECIALTY CERTIFICATION

2000- Present	Certified Nutrition Support Nurse (CNSN)
1995-1999	Trauma Nursing Core Course- Provider
1988-1999	American Association of Critical Care Nurses (CCRN)
1981-Present	Advanced Cardiac Life Support-Provider, Instructor

WORK EXPERIENCE

Oct 1996-Oct 2005	Research Nurse, The Geneva Foundation Tacoma, WA 98405
1995-1996	Staff Officer, Madigan Consolidated Education Madigan Army Medical Center Tacoma, WA 98431
1993-1995	Head Nurse, Intensive Care Unit Madigan Army Medical Center

CONSULTATION EXPERIENCE

Good Samaritan Hospital, Puyallup, WA. Critical Care / Step-down Unit Orientation ProjectJune – August 1997.
CEU-Online, Inc. Merrimack, NH 03054 Review web-based continuing medical education. December 2004, April 2003.

AFFILIATIONS AND PROFESSIONAL ORGANIZATION MEMBERSHIP

2002-Present	Sigma Theta Tau International, Member
1997-Present	Society of Critical Care Medicine, Member
1996-2000	National Nursing Staff Development Organization, Member
1993-Present	Nutrition Support Team, Madigan AMC, Member
1984-Present	American Association of Critical Care Nurses, National Member
1989-1991 & 1995-Present	American Society of Parenteral and Enteral Nutrition (A.S.P.E.N.), Member
2004-Present	A.S.P.E.N. - National Board for Nutrition Support Certification for Nurses, Member

DECORATIONS AND AWARDS

2001-2005	Biobehavioral Nursing and Health Systems Training Grant for doctoral studies in Nursing Science (NIH)
1999	AACN Wyeth-Ayerst Nursing Fellows Reporter Program
1996	Army Meritorious Service Medal (2nd OLC) Madigan AMC, Tacoma, WA 98431

PUBLICATIONS

Serna, E. & McCarthy, M.S. (2006) Evidence-based practices to prevent aspiration in enterally fed patients. *Nursing 36,* 76-77.

Loan, L.A., Brosch, L.R., McCarthy, M.S., and Patrician, P.A. (2005). Designing and implementing a database depicting quality of nursing care and staffing effectiveness. *Army Medical Department Journal*, Jul-Sep: 50-58.

McCarthy, M.S. (2005). Pulmonary Failure. In G. Cresci (Ed.) *Nutrition Support for the Critically Ill Patient: A guide to practice* (pp. 481-490). CRC Press, Boca Raton, FL.

McCarthy, M.S. (2003). Changing perspectives of stress ulcer prophylaxis. *CME-Today*, Special Report (June),*1*(1):15-22.

Martindale, R.G.& McCarthy, M.S. (2003). Optimizing acid suppression: Managing your patients in the critical care setting. *CME-Today*, Special Report (June),*1*(1):15-22. (Companion CD-ROM)

McCarthy, M. & Deal, L. (2002). Nutrition support in respiratory failure. In S. Shikora, R. Martindale, and S. Schwaitzberg (Eds.) *Nutritional Considerations in the Intensive Care Unit: Science, Rationale, and Practice* (pp. 187-199). Dubuque, Iowa: Kendall/Hunt Publishing Company.

McCarthy, M., Fabling, J., & Bell, D. (2002). Drug-Nutrient Interactions. In S. Shikora, R. Martindale, and S. Schwaitzberg (Eds.) *Nutritional Considerations in the Intensive Care Unit: Science, Rationale, and Practice* (pp. 153-175). Dubuque, Iowa: Kendall/Hunt Publishing Company.

Churley-Strom, R. & McCarthy, M. S. (2001). Role as Performance Coach. In A.E. Avillion (Ed.), *Core Curriculum for Staff Development*, (pp. 561-578), Second Edition. Pensacola, Florida: National Nursing Staff Development Organization.

McCarthy, M.S. & Brosch, L.R. (2000). Evidence-based nursing interventions to improve ARDS patient outcomes. *American Journal of Nursing*, May (Suppl), 28-32.

McCarthy, M.S. (2000). Use of indirect calorimetry to optimize nutrition support and assess physiologic dead space in the mechanically ventilated patient: A case study approach. *AACN Clinical Issues, 11*(4): 619-630,

McCarthy, M.S. (1994). Autonomic, behavioral, and self-reported assessment of pain in a selected ED population before and after parenteral analgesia. Emergency Nurses Assoc. Scientific Assembly Abstracts, *Journal of Emergency Nursing*, 20(2): 160-161.

McCarthy, M.S. (1988). Early postoperative jejunal feedings with gastric decompression: Implications for nursing practice. *Nutritional Support Services*, 8(9): 8-9.

Martindale, R.G. & McCarthy, M.S. (1988). Enteral and parenteral nutrition in the trauma patient. *Trauma Quarterly*, 4(4): 47-58.

UNPUBLISHED MANUSCRIPTS

McCarthy, M. (1989). Potassium chloride supplementation by feeding tube: Serum analysis and patient tolerance. Master's Thesis, University of Washington, School of Nursing.

PRESENTATIONS

Aging and the Immune System. Graduate level program lecture. University of Washington School of Nursing, November 22, 2005.

Inflammation and Wound Healing. Master's Entry Level Program lecture. University of Washington School of Nursing, August 15, 2005.

Perioperative Immunonutrition in Head and Neck Cancer (2004, January; 2005, May). BioBehavioral Nursing and Health Systems Seminar, University of WA, Seattle, WA.

Practical Uses of Indirect Calorimetry in the Clinical Setting (2003, February). South Sound Dietetics Association, Tacoma General Hospital.

Acute Pancreatitis (2000, 2001, November). Army's Licensed Practical Nurse Course, Madigan AMC, Tacoma, WA. 98431

Improving ALI/ARDS Patient Outcomes with Metabolic Support (2000, November). Pacific Lutheran University and Sigma Theta Tau Research Conference, Parkland, WA.

Cellular Nutrition. Intensive Care Nursing Course. Madigan Army Medical Center, 1995 – 2004 (Qtrly).

Capitalizing on Opportunities for Staff Development and Patient Education: Contributions of the Research Nurse (1999, July). National Nursing Staff Development Organization's Tenth Anniversary Celebration and Convention, Washington, DC.

McCarthy, M. and Chilton, J. (1999, February). Standard orders and indirect calorimetry enhance nutritional support of critically ill patients. Poster session at the A.S.P.E.N. 23rd Clinical Congress, San Diego, CA.

McCarthy, M. and Clark, S. (1997, August). Gastric/Jejunal Feeding: Nutritional Outcome and Pneumonia. Poster session at the TriService Nursing Research Dissemination Conference,
Bethesda, MD.

RESEARCH EXPERIENCE

Perioperative Immunonutrition in Head and Neck Cancer. Principal Investigator/Project Director. Grant funding provided by TriService Nursing

Research Program and the Hester B. McLaws Nursing Scholarship Fund University of Washington School of Nursing. Period of award: April 2004 – June 2006, $39,111.

Establishing a Military Nursing Outcomes Database: Analysis and Expansion. Project Director. Grant funding provided by TriService Nursing Research Program. Period of award: October 2003 – March 2006, $1,224,899.

Establishing a Military Nursing Outcomes Database. Project Director. Grant funding provided by TriService Nursing Research Program. Period of award: July 2002 – March 2004, $624,801.

The Use of Body Fat Analysis and Severity of Illness to Determine Energy Expenditure in the Obese Critically Ill Patient. Principal Investigator. Grant funding provided by AACN and Datex-Ohmeda Corporation. Period of award: July 2001-December 2003, $5000.

Prone Position and the Pattern of Oxygenation in Patients with Acute Lung Injury and Acute Respiratory Distress Syndrome. Co-Principal Investigator. Grant funding provided by TriService Nursing Research Program. Period of award: September 2000 to August 2003, $252,000.

Improving ARDS Patient Outcomes with Metabolic Support. Principal Investigator. Grant funding provided by TriService Nursing Research Program. Period of award: July 1998 to June 2001, $228,280.

Evaluation of the clinical status and resource utilization of ventilated patients with acute respiratory failure in intensive care units via a longitudinal observational outcomes database. Site Coordinator. Grant sponsored by Kinetic Concepts, Inc. Period of award: January 1999 to December 1999.

Gastric/Jejunal Feeding: Nutritional Outcome and Pneumonia. Co-Principal Investigator. Grant funding provided by TriService Nursing Research Program. Period of award: September 1996 to September 1998, $80,000.

Pressure Ulcer Prevention: Comparing Support Surfaces. Clinical Site Coordinator. Grant funding provided by TriService Nursing Research Program. Period of award: September 1996 to December 1997, $287,886.