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# Enteral Nutrition During Multimodality Therapy in Upper Gastrointestinal Cancer Patients

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## Objective
The objective of this study was to evaluate long-term enteral nutrition support in postoperative cancer patients.

## Background
Multimodality therapy of surgical patients with upper gastrointestinal malignancies may improve survival, but often results in substantial malnutrition, immunosuppression, and morbidity. The benefits of combined inpatient and outpatient enteral feeding with standard diets or diets supplemented with arginine, RNA + ω-3 fatty acids are unclear.

## Methods
Sixty adult patients with esophageal (22), gastric (16), and pancreatic (22) lesions were stratified by disease site and percent usual weight and randomized to receive supplemental or standard diet via jejunostomy beginning on the first postoperative day (goal = 25 kcal/kg/day) until hospital discharge. Patients also were randomized to receive (n = 37) or not receive (n = 23) enteral jejunostomy feedings (1000 kcal/day overnight) for the 12- to 16-week recovery and radiation/chemotherapy periods. Plasma and peripheral white blood cells were obtained for fatty acid levels and $PGE_2$ production measurements.

## Results
Mean plasma and cellular ω3/ω6 fatty acid levels (percent composition) increased significantly ($p < 0.05$) in the arginine + ω-3 fatty acid group by postoperative day 7 (0.30 *vs.* 0.13) and (0.29 *vs.* 0.14) and continued to increase over time. Mean $PGE_2$ production decreased significantly ($p < 0.05$) from 2760 to 1600 ng/$10^6$ cells/mL at day 7 in the arginine + ω-3 fatty acid group, whereas no significant change over time was noted in the standard group. Infectious/wound complications occurred in 10% of the supplemented group compared with 43% of the standard group ($p < 0.05$); mean length of hospital stay was 16 *vs.* 22 ($p < 0.05$) days, respectively. Of the patients who received postoperative chemoradiation therapy, only 1 (6%) of the 18 patients randomized to receive tube feeding did not continue, whereas 8 (61%) of the 13 patients not randomized to tube feedings required crossover to jejunostomy nutritional support.

## Conclusions
Supplemental enteral feeding significantly increased plasma and peripheral white blood cell ω3/ω6 ratios and significantly decreased $PGE_2$ production and postoperative infectious/wound

complications compared with standard enteral feeding. For outpatients receiving adjuvant therapy, those initially randomized to oral feedings alone required rehospitalization more frequently, and 61% crossed over to supplemental enteral feedings.

Multimodality therapy of surgical patients with upper gastrointestinal malignancies of the esophagus, stomach. and pancreas appears to improve long-term survival, but often results in substantial malnutrition, immunosuppression, and morbidity. In cancer patients undergoing surgical extirpation of tumor, the combination of malnutrition and immunodeficiency is a major predictor of postoperative complications, including poor wound healing, higher rates of infection, and a prolonged hospital length of stay. Adverse metabolic and immunologic consequences of major operation are determined by the magnitude of the operation, the use of blood transfusions, the duration of anesthesia, and associated conditions such as malnutrition.[1,2] Previously, it has been difficult to document improved surgical outcome from intravenous nutritional intervention, except in cases of the most severe preoperative malnutrition.[3–5] A large, multi-institutional Veterans Administration study demonstrated no overall improvement in clinical outcome in patients receiving a minimum of 7 days of preoperative total parenteral nutrition compared with controls.[6] In fact, infectious complications such as pneumonia were greater in those patients receiving total parenteral nutrition compared with controls. Randomized clinical trials have demonstrated improvement in clinical outcome in patients receiving enteral nutrition compared with those receiving parenteral nutrition.[7,8] For this reason, as well as to reduce cost and provide more physiologic nutritional support, enteral feeding is used much more commonly in malnourished hospitalized patients.[9]

Because of the inter-relationship between metabolic and immunologic sequelae after injury, our attention has been directed to specific nutrients that might improve immunologic function in controlled laboratory and clinical studies. Arginine is an amino acid that has major secretagogue activities, including the increased release of growth hormone, prolactin, insulin, and other hormones, such as somatomedin C.[10] Although classified as a "nonessential" amino acid, arginine's effects on new tissue growth may make it conditionally essential after injury or infectious challenge.[11] In animal studies, arginine administration improves host thymic size and cellularity, increases natural killer cell cytolytic activity, improves lymphocyte mitogenesis, enhances macrophage tumor cytotoxicity, and increases lymphocyte interleukin-2 (IL-2) production and receptor activity.[12,13] *In vivo*, supplemental dietary arginine reverses the thymolytic effect of stress, decreases the rate of tumor growth, and improves hepatic protein synthesis and T-cell responses.[13,14] Clinical studies in volunteer populations also have demonstrated improvements in T-lymphocyte responses in those who received supplemental dietary arginine compared with controls.[15]

After injury in laboratory animal models and humans, prostaglandin $E_2$ production by circulating monocytes and peritoneal macrophages is increased. Dietary supplementation with omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acid) shifts the production of prostaglandins from the dienoic prostaglandins ($E_2$) to the trienoic prostaglandins ($E_3$), the latter being much less immunosuppressive.[16] Thus, dietary supplementation with omega-3 fatty acids results in less immunosuppression through reduced production of $PGE_2$, resulting in improved T-cell function, natural killer cell activity, and macrophage IL-1 production.[17,18] Previously, a randomized clinical trial evaluated the effects of combining nutrients such as arginine, RNA, and omega-3 fatty acids, as supplements on immunologic function and clinical outcome after major operation.[19] Patients were randomized to receive the supplemented diet or a standard enteral diet after operation. *In vitro* lymphocyte mitogenesis decreased in both groups on postoperative day 1, but normal levels were regained only in the supplemented diet group at day 7. Infectious and wound complications occurred significantly less often (11%) in the supplemented group compared with the standard group (37%; $p = 0.02$). This study had a relatively short duration (<28 days) of enteral feeding.

Thus, the purpose of this current study was to evaluate the longer-term effects of a diet supplemented with arginine, RNA, and omega-3 fatty acids compared with a standard enteral diet when administered postoperatively to patients who had undergone major operation for upper gastrointestinal malignancies. Clinical outcome, white blood cell fatty acid composition, and $PGE_2$ secretion were the major endpoints in this study. At the time of initial randomization, patients were allocated to groups that were to receive or not receive additional tube feedings (approximately 1000 kcal/day) as outpatients after their discharge from the hospital. Current protocols

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**Table 1. DIET COMPOSITION PER LITER**

| | Supplemented Diet* | Standard Diet† |
|---|---|---|
| Total protein (g) | 59 | 62 |
| Intact protein | 43 | 62 |
| Free L-arginine | 13 | — |
| Total lipids (g) | 28 | 49 |
| Medium chain triglycerides | 7 | 14 |
| Linoleic acid | 2.2 | — |
| Eicosapentaenoic acid and docosahexenoic acid | 1.7 | — |
| Carbohydrates (g) | 132 | 107 |
| RNA (g) | 1.25 | — |

* Impact, Sandoz Nutrition, Minneapolis, MN.
† Traumacal, Bristol-Meyers Squibb, Evansville, IN.

in use in our institution use postoperative adjuvant radiation therapy and chemotherapy, particularly for those patients who have primary esophageal and pancreatic malignancies. Thus, this portion of the study was designed in a pilot fashion to assess the effects of additional tube jejunostomy feedings plus oral feeding in the outpatient setting, compared with oral intake alone.

## MATERIALS AND METHODS

Sixty adult patients with upper gastrointestinal malignancies who underwent major abdominal operation were eligible for entry into the study if they achieved the following criteria: no history of intestinal disease precluding feeding, no previous abdominal or pelvic radiotherapy, no preoperative evidence of infection (temperature > 37.6 C, white blood cell count > 10,000 cells/mL or bacteremia), and no administration of steroids or other immunosuppressive medications. Normal renal (serum creatinine ≤ 1.5 mg/dL) and hepatic function (total serum bilirubin ≤ 1.5 mg/dl) were required. General assessment of nutritional status included measurements of height and body weight and a description of usual and ideal body weight. All patients gave informed consent to this study, which was approved by the Institutional Review Board of the University of Pennsylvania School of Medicine.

Patients were stratified by the extent of their preoperative weight loss (<10% of usual body weight *vs.* ≥10% of usual body weight) and whether their primary diagnosis was esophageal and gastric *versus* pancreatic primary malignancies. Sixty patients were randomized by use of a sealed-envelope system to one of four treatment groups. One group of patients (n = 18) received enteral alimentation with the supplemented diet (Impact, Sandoz Nutrition, Minneapolis, MN; Table 1) to be given both in the hospital and as an outpatient, whereas the second group (n = 12) was to receive the supplemented diet as inpatients and receive no additional feedings during the outpatient period. The third group of patients (n = 19) received enteral alimentation with the standard enteral diet (Traumacal, Bristol-Meyers Squibb, Evansville, IN; Table 1) during hospitalization and as an outpatient, whereas the fourth group of patients (n = 11) received the standard enteral diet as an inpatient, but received no additional feedings as an outpatient.

All patients had operative procedures performed by two staff surgeons (JMD and EFR) as the primary site and stage of disease indicated (Table 2). The primary diagnoses were similar between groups. At the time of operation, a Witzel tube jejunostomy with a #12 or #14 French rubber catheter was placed in the proximal jejunum. Five percent dextrose and water was infused continuously by pump immediately after operation through the tube jejunostomy at a rate of 30 mL/hr. Blood and fluids were replaced intravenously as clinically indicated for each patient. On the first postoperative day, patients began their respective enteral diets. Jejunostomy infusion was initiated with full-strength feedings at 25 mL/hour and then increased to the optimal goal (75–100 mL/hr) by the third postoperative day. The diet progression plan was intended to provide approximately 25 cal/kg/day. Patients were continued on their enteral supplements via jejunostomy tube at these rates until they were able to take fluids and food by mouth. For those patients

**Table 2. PATIENT CHARACTERISTICS**

| | Supplemented Diet | Standard Diet |
|---|---|---|
| No. of patients | 30 | 30 |
| Age (yr) | 61 ± 12 | 61 ± 10 |
| Gender (M/F) | 25/5 | 16/14 |
| Operative procedures | | |
| Esophagogastrectomy | 14 | 13 |
| Gastrectomy | 6 | 5 |
| Pancreatectomy | 6 | 9 |
| Other | 4 | 3 |
| Pathologic stage | | |
| I | 7 | 2 |
| II | 5 | 8 |
| III | 9 | 14 |
| IV | 6 | 4 |
| Body weight ≤ 10% usual body weight | 12 | 10 |
| Initial serum albumin (g/dL) | 3.3 ± 0.6 | 3.2 ± 0.5 |
| Initial serum transferrin (mg/dL) | 200 ± 54 | 208 ± 54 |
| Operative time (min) | 363 ± 119 | 360 ± 106 |
| Estimated blood loss (mL) | 1619 ± 1122 | 1517 ± 1347 |
| Total units transfused | 2.9 ± 2.4 | 2.5 ± 2.4 |

Mean ± SD

who continued tube feedings in outpatient settings, enteral supplements were cycled so that they would receive approximately 1000 kcal/day given over a 12-hour period from 7:00 P.M. to 7:00 A.M. After cessation of enteral feedings, the jejunostomy catheters were flushed daily with water. Those patients randomized to continue enteral feedings at home received their respective enteral diets in this cycled fashion, starting at the time of discharge. Patients and their families were instructed on methods of continuous pump enteral jejunostomy feedings while at home, to be used as a supplement each evening. Home nursing outpatient support was provided to help in this transition from inpatient to outpatient settings.

Patients randomized to receive additional enteral feedings in the outpatient setting were planned to continue this for a period of 12 to 16 weeks after discharge, depending on the initiation and completion of their radiation and chemotherapy. Radiation therapy dosages ranged from 5256 to 6000 cGy encompassing mediastinal and upper abdominal areas as dictated by the primary tumor site. Chemotherapy generally was administered during the first and last weeks of radiation therapy and consisted of 96-hour infusions of 5-fluorouracil with leucovorin.

Patients randomized to receive additional tube feedings while at home were deemed to have crossed over to the opposite group when they discontinued their tube feedings permanently or for greater than 5 consecutive days. Patients randomized to oral feeding only were deemed to have crossed over to the tube feeding group when jejunostomy tube feedings were initiated and continued for greater than 5 days. Automatic crossover of these patients to tube feeding occurred if individuals were unable to take in food by mouth or greater than 10% body weight loss occurred during the time of outpatient adjuvant therapy.

Perioperative complications were tabulated prospectively and were determined in a blinded fashion retrospectively to ensure definition consistency. Infectious complications consisted of pneumonia (radiographic confirmation and documentation of pathologic organisms in sputum), wound (erythema, swelling, pus in wound), abdominal (operative or spontaneous drainage of an abdominal purulent collection), and systemic (fever [oral temperature > 38.5°C] and positive blood culture for pathogenic organisms). Wound complications consisted of wound dehiscence, anastomotic leak, and fistula. Gastrointestinal symptoms were assessed and recorded daily. If moderate to severe symptoms of nausea, vomiting, abdominal cramping, or diarrhea occurred, infusion was discontinued for 8 to 12 hours and then resumed at a lower infusion rate when possible. Adverse symptoms were managed as clinically indicated, so diarrhea and cramping were treated with enteral codeine, loperamide hydrochloride (Imodium, Janssen Pharmaceutica, Inc., Piscataway, NJ), or tincture of opium, when appropriate. When there were adverse symptoms, they were recorded for each day; this included nausea or vomiting that required anti-emetics, diarrhea of at least 3 to 5 loose bowel movements per day, abdominal cramping or bloating that limited ambulation and was unrelated to flatus, pain that was relieved only by medication and was distinct from pain of an incision, and fever that was defined as an oral temperature of more than 38.5 C.

All patients received perioperative intravenous cephalosporin antibiotics, which started before operation and continued for 24 hours after surgery. Patients were managed by use of $H_2$ blockers and nasogastric tubes, which were removed when clinically indicated. Patients generally received no oral nutrition during the first 7 postoperative days. Patients undergoing esophagogastrectomy underwent a meglumine diatrizoate (Gastrografin, Bristol-Meyers Squibb, Princeton, NJ) swallow on postoperative day 7, before initiation of oral intake. All patients received intravenous fluids (5% dextrose/0.5% normal saline solution) and other electrolytes as clinically indicated.

## Analytical Studies

Body weight and enteral tube feeding intake of calories and nitrogen were determined for all patients daily for the first 7 days while patients took nothing by mouth. Blood was obtained preoperatively, on the first postoperative day, and at 1, 2, and 4 weeks for determination of serum and cellular fatty acid levels. At the time of blood sampling, peripheral white blood cells were obtained for lipid composition measurement.

Human white blood cells were isolated from sodium citrate-anticoagulated venous blood of patients. Phospholipids of replicate pellets of white blood cells were extracted with chloroform: methanol (2:1,v:v) and the fatty acids released and esterified by treatment with 6% HCl in methanol (v:v) for 60 minutes at 70°C. Arachidonic acid, eicosapentaenoic acid and docosahexaenoic acid were resolved by high-performance liquid chromatography on a 0.4 × 25-cm octadecylsilane column developed with methanol: water (90:10, vol/vol) at 1 mL/min and were quantified by absorption at 214 mm; the quantities in representative samples were confirmed by gas chromatography. Prostaglandin $E_2$ in aqueous suspensions of solid-phase extracts was quantitated by radioimmunoassay (Seragen, Inc., Boston, MA) as basal amounts and amounts stimulated by lipopolysaccharide ([LPS]; 10 μg/mL).

## Statistical Methods

The study was a randomized clinical trial. The sample size was selected to detect a 50% difference in complications based on results from a previous randomized clinical trial. The data analysis used unpaired Student's t test, chi square analysis with Fisher exact test, and life-table analysis. The Kaplan-Meier method was used to assess hospital length of postoperative stay. Length of stay was not adjusted (or censured) to reflect other medical conditions present before surgery, newly developed during feeding, or present after the end of feeding. A p value of less than 0.05 was required for statistical significance. Data are expressed as a mean ± the standard deviation.

## RESULTS

### Patient Characteristics and Nutritional Results

As shown in Table 2, 60 patients were studied. There were 30 patients in the supplemented diet group and 30 patients in the standard diet group. The mean age (61 years) was identical in both groups. The gender distribution, types of operative procedures, and pathologic stages of disease were not significantly different comparing the two groups. In the supplemented diet group, 12 of 30 patients had experienced ≥10% usual body weight loss before study entry, compared with 10 of 30 patients in the standard diet group. Initial mean serum albumin and serum transferrin concentrations were similar between groups.

The magnitude of operative injury was assessed by measurement of operative time, estimated blood loss, and the total units of blood transfused within the 24-hour perioperative period. The mean operative time was 363 ± 119 minutes in the supplemented diet group compared with 360 ± 106 minutes in the standard diet group. The mean estimated blood loss and the mean total units of blood transfused in the 24-hour perioperative period also were similar between groups.

As shown in Table 3, nutritional characteristics also were similar between groups. Initial mean body weight was 72 ± 14 kg in the supplemented diet group compared with 66 ± 12 kg in the standard diet group. Mean serum prealbumin (mg/dL), albumin (g/dL), and transferrin (mg/dL) levels were similar between groups. Mean caloric intake per day was 1067 ± 335 kcal in the supplemented group for the first 7 days after the operative procedure compared with 1234 ± 372 kcal in the standard diet group during the same period. Mean nitrogen intake per day was 11.9 ± 4.1 g in the supplemented group compared with 10.1 ± 3.1 g in the standard diet group. Mean prealbumin, albumin, and transferrin concentrations at day 14 also were similar in both groups of patients (Table 3).

**Table 3. NUTRITIONAL CHARACTERISTICS**

| | Supplemented | Standard |
|---|---|---|
| Initial body weight (kg) | 72 ± 14 | 66 ± 12 |
| Caloric intake/day* | 1067 ± 335 | 1232 ± 372 |
| Nitrogen intake/day* | 11.9 ± 4.1 | 10.1 ± 3.1 |
| Serum Proteins | | |
| Prealbumin (mg/dL) | | |
| Preoperative | 19 ± 5 | 10 ± 7 |
| Day 14 | 16 ± 7 | 17 ± 4 |
| Albumin (g/dL) | | |
| Preoperative | 3.3 ± .6 | 3.2 ± .5 |
| Day 14 | 3.1 ± .4 | 3.1 ± .4 |
| Transferrin (mg/dL) | | |
| Preoperative | 200 ± 54 | 208 ± 54 |
| Day 14 | 190 ± 60 | 181 ± 53 |

* Over 7 days.
Mean ± SD.

### Plasma and White Blood Cell Fatty Acid Concentrations

Mean plasma arachidonic acid concentrations (% composition) were quite similar between groups at all time periods measured, as shown in Figure 1. In the supplemented diet group, mean plasma arachidonic acid levels decreased from 11.2% ± 1.7% preoperatively to 7.8% ± 1.6% at postoperative day 28. In the standard-fed group, mean plasma arachidonic acid levels were 10.9% ± 2.0% preoperatively and were 10.3% ± 4.6% at postoperative day 28. As shown in Figure 2, mean plasma eicosapentaenoic acid levels increased significantly in the supplemented diet group from 0.51% ± 0.19% preoperatively to 5.0% ± 2.4% at postoperative day 28. The most dramatic rise occurred in the first 7 postoperative days because the mean plasma eicosapentaenoic level was 3.6% ± 2.2% at postoperative day 7. In contrast, mean plasma eicosapentaenoic acid levels increased only slightly in the standard-fed group, from 0.62% ± 0.28% preoperatively to 1.1% ± 0.8% at postoperative day 28. Mean plasma docosahexaenoic acid levels increased somewhat in the supplemented group, from 3.85% ± 1.49% preoperatively to 5.07% ± 1.37% at postoperative day 28. There was no significant difference between the mean preoperative and postoperative day 28 docosahexaenoic acid level in the standard diet group (0.16% ± 0.04%). With the aforementioned changes in individual fatty acids, the mean plasma omega-3 to omega-6 fatty acid ratio increased significantly in the supplemented diet group, from 0.15 ± 0.05 preoperatively to 0.43 ±

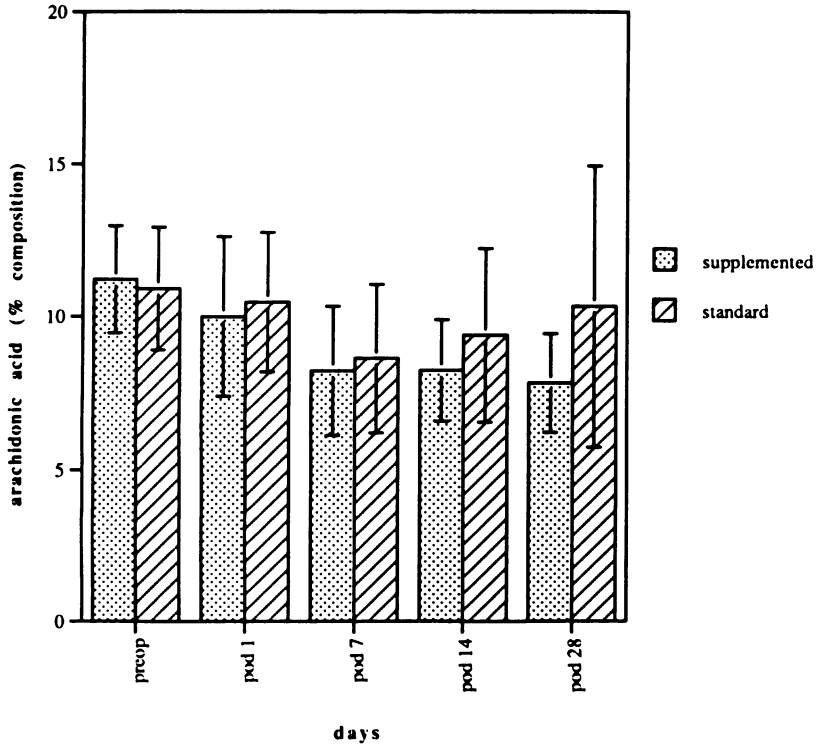



**Figure 1.** Mean (±SD) plasma arachidonic acid levels over time were similar between groups.

0.12 on postoperative day 28 (Fig. 3). In contrast, the mean plasma omega-3 to omega-6 fatty acid ratio remained stable in the standard-fed diet group (0.16 ± 0.04 preoperatively to 0.15 ± 0.10 at postoperative day 28).

The changes in the mean plasma fatty acid levels were reflective of those in cellular phospholipid composition. Mean cellular arachidonic acid levels remained similar over time in both the supplemented

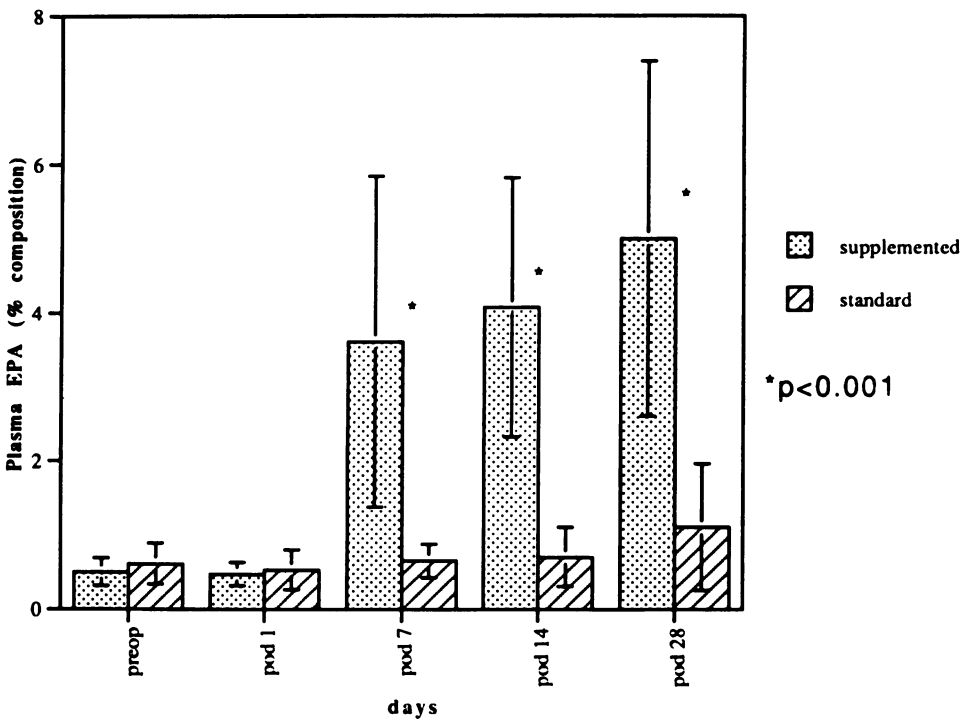



**Figure 2.** Mean plasma eicosapentaenoic acid levels increased significantly in the supplemented group by postoperative day 7.

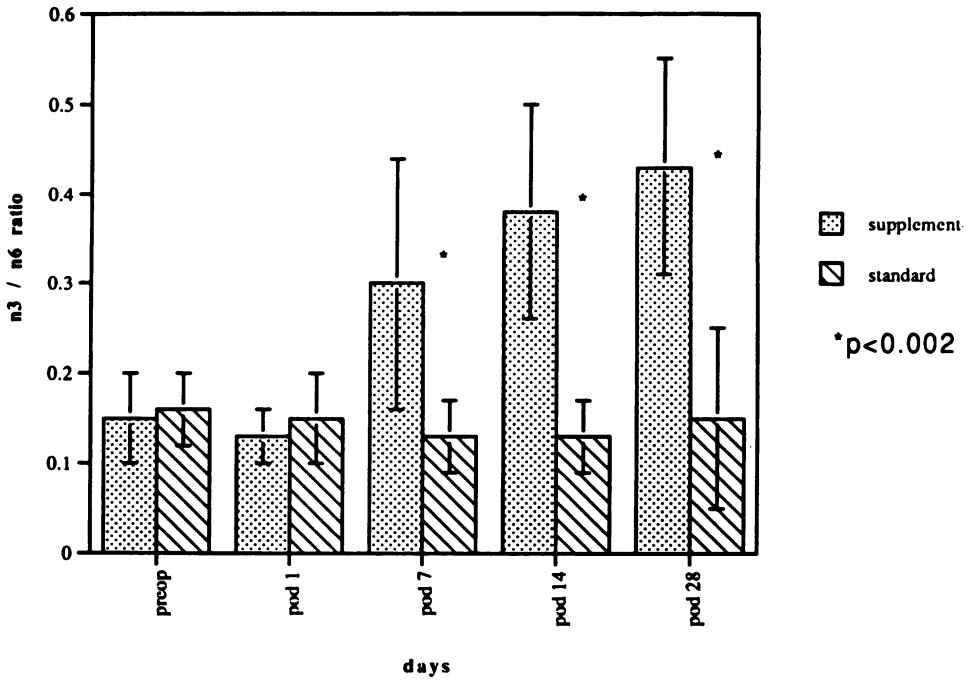



**Figure 3.** Mean plasma ω3/ω6 ratio increased significantly in the supplemented group by postoperative day 7.

and standard diet groups, varying from 11% to 15%. As shown in Figure 4, mean cellular eicosapentaenoic acid levels increased significantly from 0.42% ± 0.11% preoperatively to 2.4% ± 1.3% at postoperative day 28 in the supplemented group. Mean cellular docosahexaenoic acid levels increased significantly from 1.55% ± 0.67% preoperatively to 2.46% ± 0.56% at postoperative day 28 in the supplemented group, with no significant changes found in the standard group. Consequently, the omega-3 to omega-6 cellular fatty acid ratio increased significantly from 0.16% ± 0.04% preoperatively to 0.33% ± 0.08% at postoperative day 28 (Fig. 5). In contrast, in the patients fed the standard diet, mean cellular omega-3 to omega-6 fatty acid ra-

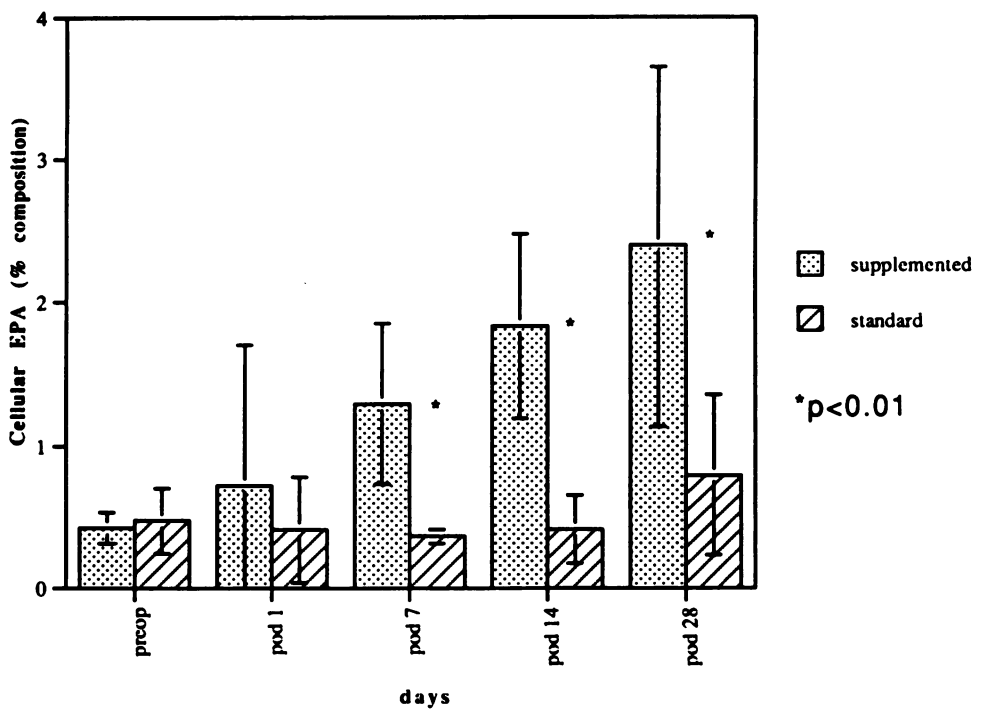



**Figure 4.** Mean cellular eicosapentaenoic acid levels increased significantly in the supplemented group by day 7.

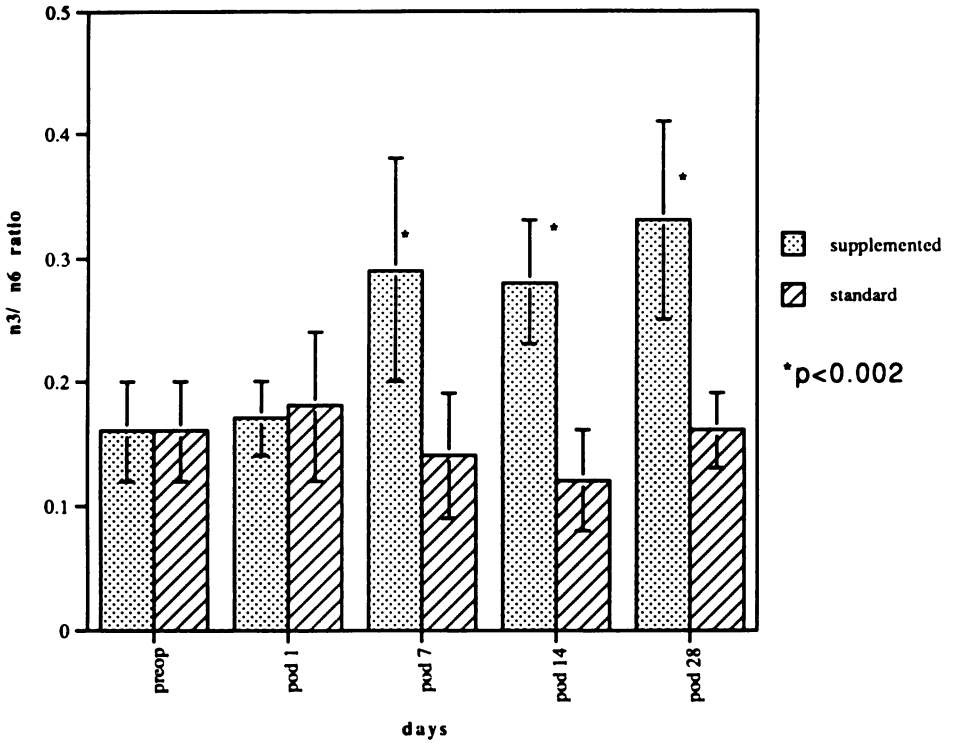



**Figure 5.** Mean cellular ω3/ω6 ratio increased significantly in the supplemented group by postoperative day 7.

tios were identical preoperatively and on postoperative day 28 (0.16% ± 0.04%).

Mean basal $PGE_2$ concentrations in the standard diet-fed group varied from 203 pg/mL to 1650 pg/mL, with no discernible change over time. In contrast, basal $PGE_2$ levels in the supplemented diet group decreased significantly from 2760 ± 1640 pg/mL preoperatively to 892 ± 492 pg/mL at postoperative day 28, as shown in Figure 6. Mean stimulated $PGE_2$ levels in the standard-fed group varied from 678 to 2438 pg/mL without a pattern of change. However, in the supplemented diet group, mean stimulated $PGE_2$ levels decreased from 2106 ± 1519 pg/mL preoperatively to 1335 ± 359 pg/mL at day 28.

## Clinical Outcome

Postoperative complications were classified as infectious (pneumonia, wound, abdominal, and systemic) and wound healing (fistula, anastomosis, and incision dehiscence) complications. Shown in Table 4, the number of infections and wound complications was evaluated for each patient group according to criteria that had been designed before the onset of the study. Patients were defined as ineligible if they were found to have a criteria which deemed them ineligible after randomization. Two patients given the standard diet were placed on steroids postoperatively for substantial exacerbations of asthma and chronic obstructive pulmonary disease and were excluded under the eligible analysis category. Subgroup analysis was performed against criteria designed before the study, but no statistical comparisons were made between subgroups. The major analysis was that of all patients who were randomized with intent to treat (total =

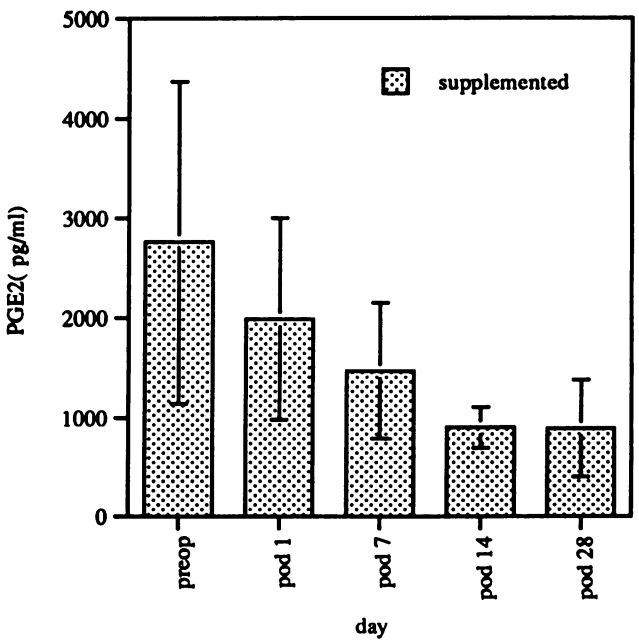



**Figure 6.** Mean $PGE_2$ secretion decreased significantly over time in the supplemented patient group.

**Table 4. Infections/Wound Complications**

| Standard Diet | | | | |
|---|---|---|---|---|
| **Intent to Treat (n = 30)** | **Eligible (n = 28)** | **Eligible + Complications > 72 hr (n = 25)** | **Eligible + 600 Kcal (n = 22)** | **Eligible + Both (n = 20)** |
| Pneumonia | + | + | + | + |
| Pneumonia | + | + | + | + |
| Pneumonia | — | — | — | — |
| Anastomotic fistula | + | + | + | + |
| Anastomotic fistula | + | + | + | + |
| Abscess + anastomotic leak | + | — | — | — |
| Ischemic bowel* | + | — | + | — |
| Pneumonia/wound infection | + | — | + | — |
| Bile leak w/bile peritonitis | + | + | + | + |
| Subphrenic abscess | + | + | + | + |
| Pneumonia | + | + | — | — |
| Gastric necrosis/perforation* | + | + | — | — |
| Inspissated TF w/pathologic Patchy bowl necrosis + pneumonia | + | + | + | + |
| 13/30 (43%) | 12/28 (42%) | 9/25 (36%) | 9/22 (40%) | 7/20 (35%) |

| Supplemented Diet | | | | |
|---|---|---|---|---|
| **Intent to Treat (n = 30)** | **Eligible (n = 30)** | **Eligible + Complications > 72 hr (n = 29)** | **Eligible + 600 Kcal/day (n = 29)** | **Eligible + Both (n = 29)** |
| Cholangitis | + | + | + | + |
| Bile leak | + | + | + | + |
| Anastomotic fistula | + | + | — | — |
| 3/30 (10%)† | 3/30 (10%) | 3/30 (10%) | 2/29 (6%) | 2/29 (6%) |

+ Complication.
— Excluded in this category.
* Patient also had sepsis and adult respiratory distress syndrome.
† $p < 0.005$.

60 patients). Patients who developed major complications within 72 hours of the operative procedure were examined as a separate category, as were patients who were not able to receive an average of 600 kcal/day for 4 of the first 7 days. Finally, an analysis category was designed to evaluate patients who were declared eligible who developed complications more than 72 hours after operation and who received at least 600 cal/day for 4 of the first 7 postoperative days. Shown in Table 4 are the complications as outlined under these analysis subgroups. In the supplemented diet group, 3 of 30 patients (10%) developed major postoperative infections and wounds (cholangitis, bile leak, and anastomotic fistula). This was significantly less ($p < 0.005$) than 13 of 30 patients (43%) who developed complications and were given the standard diet. Reduction in postoperative complications was noted in each of the subgroups comparing the supplemented with the standard-fed group. Mean hospital length of stay was 16 ± 0.9 days in the supplemented diet group compared with 22 ± 2.9 days in the standard diet group. Analysis of length of stay using Mantel-Cox and Tarone-Ware testing showed p values equal to 0.02 and 0.03. There was one inpatient death in the supplemented diet group compared with two deaths in the standard diet group.

Gastrointestinal complications generally were mild and infrequent, except when diarrhea was the complication measured. Diarrhea for ≥3 days occurred in 17 of 30 patients in the supplemented diet group (57%) compared with 14 of 30 patients in the standard diet group (46%). Vomiting occurred in only 3 of 30 (10%) and 4 of 30 (13%) patients in each of the two respective groups.

## Outpatient Therapy

As shown in Figure 7, at the time of hospital discharge, patients were determined to either receive (37)

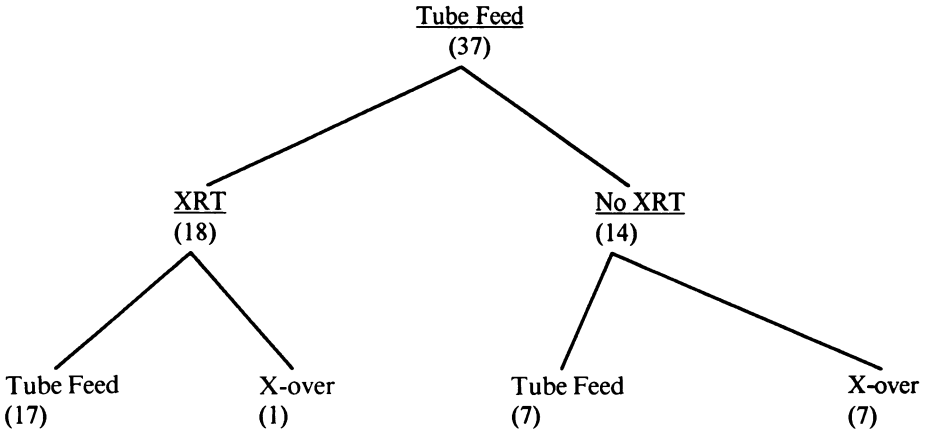
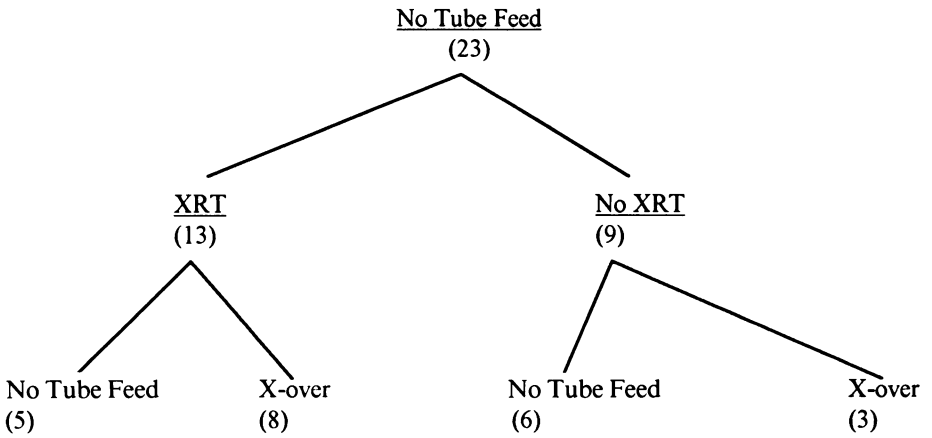



**Figure 7.** Randomized schema and outcome for outpatient tube feeding with or without adjuvant therapy.




or not receive (23) tube feeding as part of their initial randomization. Adjuvant chemotherapy and radiation therapy was indicated and was accepted by 31 patients. Of the remaining 29 patients, 11 began their adjuvant treatment after the 12-week study period and 12 received no adjuvant treatment. Six patients were not included in the outpatient analysis either because of inpatient death (3), crossover to total parenteral nutrition in the hospital (1), and use of steroids (2). Thus, of the 37 patients who were randomized to the outpatient tube feeding group, 18 received adjuvant chemotherapy and radiation therapy. Of these 18 patients, 17 continued on tube feedings throughout the course of their adjuvant therapy, and tube feeding was discontinued after cessation of their adjuvant treatment, usually by postoperative week 12. Only 1 of 18 patients (6%) discontinued tube feeding during this period. In the patients randomized to tube feeding who did not receive adjuvant therapy with radiation and chemotherapy, 7 of 14 patients continued to be fed throughout the 12-week period of time as they regained their appetite and strength.

Twenty-three patients were randomized to oral feeding alone during the outpatient period. Thirteen of these patients received adjuvant chemotherapy and radiation therapy, and eight patients (61%) crossed over and began to receive tube feeding because of complications of diarrhea, dehydration, inanition, or other problems that occurred during radiation and chemotherapy. In those patients who did not receive radiation therapy and chemotherapy, six of nine continued to receive all of their nutrition orally.

In the 31 patients receiving adjuvant chemotherapy and radiation therapy in the outpatient setting, the group randomized to supplemental jejunostomy feedings had a decreased requirement for rehospitalization (1/18 = 6%) compared with 5 of 13 (37%) of the patients who did not initially receive tube feeding.

## DISCUSSION

Major injury and operation results in significant postoperative metabolic alterations and down-regulation of host immune defense mechanisms. Conditions such as patient age, presence of malignancy, blood transfusions, malnutrition, and certain drugs add to this immunosuppression to predispose the patient to increased risk of postoperative complications. Both cellular and humeral immune function are depressed after major injury. Controlled laboratory studies have demonstrated decreased nonspecific cellular functions, such as depressed macrophage IL-1, IL-6, and superoxide production, whereas prostaglandin $E_2$ production is increased.[20] Depressed T-cell proliferation, natural killer cell cytotoxicity, and macrophage cytotoxicity also have been noted in laboratory studies.[21] Recent data confirm that the neuroendocrine response to injury, which is related to the magnitude of the injury, plays a major role in perioperative immunosuppression because of both corticoid and prostanoid production.[22]

Because of the inter-relationship of injury, presence of cancer, malnutrition, and immunosuppression, our laboratory has focused on specific nutrients that enhance cellular immune function. As an amino acid, arginine simulates growth hormone, insulin, and prolactin.[10] These hormones have been demonstrated to have metabolic functions after injury and positive effects on T-cell proliferation and other cellular immune effector mechanisms.[23] Arginine has been noted to directly enhance macrophage tumor cytotoxicity through production of nitric oxide and directly increase T-cell proliferation, natural killer cell cytotoxicity, and generation of lymphokine-activated killer cells.[24,25] Thus, arginine has direct cellular effects as well as indirect hormonal effects. Previous clinical studies from our laboratory have shown that postoperative administration of arginine compared with glycine as supplements to standard enteral diets significantly improved plasma somatomedin C levels, T-cell proliferation, and helper cell ratios.[26]

In addition to arginine, Rudolph et al. noted prolonged allograft survival in animals that are administered a purine-free diet.[27] Administration of RNA, especially uracil, significantly improved survival to a septic challenge with *Candida albicans*.[28,29] In addition, more rapid return of immune function was noted in malnourished animals given RNA during protein repletion.[30]

The $\omega$-3 polyunsaturated fatty acids ($\omega$-3 PUFA)—e.g., eicosapentaenoic acid (20:5 n-3) and docosahexaenoic acid (22:6 n-3)—influence the production of prostanoids from the dienoic to the trienoic variety, the latter of which are much less immunosuppressive.[31] A major biologic effect of dietary polyunsaturated fatty acids are the changes in cell membrane composition and receptor enzyme functions. Diets high in omega-3 PUFA decrease $PGE_2$ synthesis and suppress IL-1-$\beta$ and TNF production after cellular stimulation.[32] Both animal and human studies evaluating mononuclear cells, Kupffer's cells, and peritoneal macrophages demonstrates suppression of IL-1-$\beta$ secretion by 27% to 61% after increased omega-3 fatty acids are given in the diet.[32] The lipid composition of monocytes, macrophages, and lymphocytes are altered by the fatty acid composition of dietary lipids. These cells synthesize nonessential fatty acids, but use the essential fatty acids from plasma lipids to replenish their cell membranes. Very low levels of $PGE_2$ help in the maturation of T cells, but higher levels suppress cellular function, such as the proliferative response of IL-2 dependent T cells and natural killer cell and macrophage cytotoxic activity.[33] The monocyte and macrophage are the major cells responsible for $PGE_2$ production in peripheral cells. Ertel et al. provided diets high in $\omega$-3 PUFA to mice for 3 weeks compared with dietary fat sources derived from corn oil and safflower oil.[34] In the corn oil and safflower oil groups, hemorrhage resulted in significant increases in $PGE_2$ release by peritoneal macrophages and decreases in antigen presentation, IL-1, and IL-2 release. The mice receiving diets with increased $\omega$-3 PUFA did not have an increase in $PGE_2$ and had normal antigen-presenting function. In our studies, both plasma levels and monocyte cellular omega-3 fatty acid composition increased significantly in the supplemental group, whereas $PGE_2$ secretion decreased.

Previous studies from our laboratory have demonstrated that postoperative administration of an enteral diet enriched with arginine, RNA, and omega-3 fatty acids resulted in significantly fewer complications and a shorter hospital length of stay coupled with increased T-cell proliferation on the seventh postoperative day compared with patients fed a standard diet.[19] In our current studies, nutritional outcomes, such as body weight and serum proteins, were similar between groups. Use of the supplemented diet significantly increased both plasma and peripheral monocyte omega-3/6 fatty acid ratios while decreasing basal $PGE_2$ secretion. Major outcome variables, such as infectious/wound complications and hospital length of stay, were significantly less in the supplemented diet group compared with results in controls fed a standard enteral diet.

In the outpatient setting, patients receiving tube feeding and adjuvant therapy usually (94%) continued such therapy, whereas those initially randomized to oral feeding alone (61%) more frequently crossed over to tube feeding. The patients' willingness to begin to receive tube feeding was made easier by the continued presence of the tube and may have biased the results. Nevertheless, it appears that the rate of rehospitalization was less in those patients who received tube feeding compared with

those who did not. Clinical trials in the outpatient setting are more difficult because of the heterogeneity of response to adjuvant chemotherapy and radiation therapy, radiation portal size and site for treatment, home care support by family and friends, and social and geographic issues. Studies such as these are essential to determine whether longer-term enteral nutrition support improves patient recovery and lessens postoperative adjuvant therapy complications. Clearly, larger prospective, randomized trials are necessary to assess this specific issue.

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