European Journal of Clinical Nutrition (2002) 56, 1126–1129

0954–3007/02 $25.00
www.nature.com/ejcn

ORIGINAL COMMUNICATION

# Postsurgery enteral nutrition in head and neck cancer patients

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**Objective:** Patients with head and neck cancer undergoing surgery have a high incidence of postoperative complications. The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients, using an arginine-enriched diet, could improve nutritional variables as well as clinical outcomes.
**Design:** Randomized clinical trial.
**Setting:** Tertiary care.
**Subjects:** A population of 47 patients with oral and laryngeal cancer were enrolled.
**Interventions:** At surgery patients were randomly allocated to two groups: (a) patients receiving an enteral diet supplemented with arginine and fiber (group I); (b) patients receiving an isocaloric, isonitrogenous enteral formula (group II).
**Results:** No significant intergroup differences in the trend of the three plasma proteins and lymphocytes were detected. Gastrointestinal tolerance (diarrhea) of both formulas was good (17.4% group I and 8.3% group II; NS). During the 3 months after hospital discharge five patients died; no diferences were detected between groups (13% group I and 8.3% group II; NS). The incidences postoperative infection complications were similar (nine patients) in both groups (21.7% group I and 16.7% group II; NS). Fistula were less frequent in enriched nutrition group (0% group I and 20.8% group II; $P<0.05$); wound infection was more frequent in group II, but without statistical difference (4.3% group I and 12.5% group II; NS). The length of postoperative stay was $22.8 \pm 11.8$ days in the enriched group and $31.2 \pm 19.1$ days in the control group ($P=0.07$).
**Conclusions:** In conclusion, enriched formula improves local wound complications in postoperative head and neck cancer patients. Our results suggest that these patients could benefit from an immunonutrient-enhanced enteral formula.
*European Journal of Clinical Nutrition* (2002) **56,** 1126–1129. doi:10.1038/sj.ejcn.1601458

**Keywords:** enteral nutrition; head and neck cancer; surgery

## Introduction

Patients with head and neck cancer undergoing surgery have a high incidence of postoperative complications (Arriaga *et al*, 1990). These complications include anastomotic fistula, wound infection and major complications such as septicemia, and may lead to a prolonged hospital stay.

It is known that the immune system is frequently affected in these patients. Also, surgery and malnutrition (which is frequent in these patients) have been found to depress the immune system (Van Bokhorst-de van der Schueren *et al*, 1998).

Alterations in the host defense mechanisms make patients susceptible to complications. Although immune dysfunction could be multifactorial, the immune system may be modulated by specific nutritional substrates, such as arginine (Daly *et al*, 1998). There is evidence suggesting that enteral nutrition, supplemented with different agents including arginine and dietary fiber, improves immune function and reduces postoperative complications, in different groups of patients, such as those undergoing pancreatic surgery (Di Carlo *et al*, 1999), surgery for stomach and colo-rectum cancer (Gianoti *et al*, 1999; Wu *et al*, 2001), and critically ill patients (Caparros *et al*, 2001).

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Received July 2001

The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients, using an immunonutrition diet, could improve nutritional variables as well as clinical outcomes, postoperative infections, wound complications and length of stay, when compared with an isonitrogenous, isocaloric control enteral diet.

## Material and methods

### Patients

A population of 47 patients with oral and laryngeal cancer was enrolled. Exclusion criteria included: severely impaired hepatic function (total bilirubin concentration $>3.5$ mg/dl) and renal function (serum creatinine concentration $>2.5$ mg/dl); ongoing infections; autoimmune disorders; steroid treatment; nutritional oral supplementation in the previous 6 months; and severe malnourishment (weight loss >10% of body weight). The study was a prospective randomized trial carried out from March 1999 to July 2001. Baseline studies on all patients consisted of taking a complete history and physical examination. General assessment of nutritional status included measurements of height, body weight and body mass index (BMI; kg/m$^2$).

### Nutrition

At surgery patients were randomly allocated to two groups: (a) patients receiving an enteral diet supplemented with arginine and dietary fiber (group I); (b) patients receiving an isocaloric, isonitrogenous enteral formula (group II). The main investigator and patients remained blind to the treatment group. Table 1 shows the composition of the two enteral diets. Enteral feeding was started within 24 h of surgery at a rate of 20 ml/h, via an intraoperatively placed nasogastric tube. The infusion rate was progressively increased every 24 h until the daily nutritional goal (32 total kcal/kg; 1.7 g protein/kg) was reached, on postoperative day 4. All patients reached 100% of calculated requirements. Any drop-outs were present in the study. The endpoint for nutritional support was a minimum oral intake of 1500 cal/day and 1 g/kg/day of protein without supplementation with a minimun of 10 days of enteral support.

**Table 1** Composition of enteral diet (per 100 ml)

| | Group I (immunonutrition) | Group II (standard) |
|---|---|---|
| Total energy (kcal) | 125 | 125 |
| Protein (g) | 6.22 | 6.25 |
| Free L-arginine | 0.625 | — |
| Casein | 5.595 | 6.25 |
| Total lipid (g) | 4.86 | 4.86 |
| W6/w3 | 5/1 | 5/1 |
| Linoleic acid | 1.18 | 1.25 |
| α-linolenic acid | 0.23 | 0.25 |
| Carbohydrate (g) | 13.58 | 14.11 |
| Dietary fiber (g) | 0.9 | — |

Dietary fiber: oligofructose, inulin, soy polysaccharide, resistant starch, arabic gum and cellulose.

Prophylactic antibiotic treatment was given for 7 days postoperatively (ceftazidime, 500 mg three times daily i.v. and clyndamicine 300 mg three times daily i.v.).

### Patient monitoring

Perioperatively and on postoperative days 7 and 14 the following parameters were evaluated: serum values of prealbumin (mg/dl), transferrin (mg/dl), albumin (g/dl) and total number of lymphocytes ($10^6$/ml). Postoperative complications were recorded as none, general infections (respiratory tract infection was diagnosed when the chest radiograhic examination showed new or progressive unfiltration, temperature above 38.5°C and isolation of pathogens from the sputum or blood culture and/or urinary tract infection was diagnosed if the urine culture showed at least $10^5$ colonies of a pathogen) and local complications such as fistula and/or wound infection, assessing all complications using standard methods and the same investigator. Gastrointestinal problems related to enteral feeding were also recorded (diarrhea, >5 liquid stools in a 24 h period or an estimated volume $>2000$ ml/day). Mortality was assessed 3 months after hospital discharge.

### Assays

Fasting blood samples were drawn for measurement of albumin (3.5–4.5 g/dl), prealbumin (18–28 mg/dl), transferrin (250–350 mg/dl), and lymphocytes (1.2–3.5.10$^3$/μl) with an autoanalyzer (Hitachi, ATM, Manheim, Germany).

### Statistical analysis

Sample size was calculated to decrease fistula complication by 20% with 80% power and 5% significance. The results were expressed as average ± standard deviation. The distribution of variables was analyzed with a Kolmogorov–Smirnov test. Quantitative variables with normal distribution were analyzed with two-tailed paired or unpaired Student's *t*-test, as needed, and analysis of variance (ANOVA). Non-parametric variables were analyzed with the Friedman and Wilcoxon tests. To minimize the potential for introducing bias, all randomized patients were included in the comparisons, irrespective of whether or not and for how long they complied with their allocated regimen (intention-to-treat analysis). A $P$-value $<0.05$ was considered statistically significant.

## Results

Forty-seven patients were enrolled in the study. The mean age was 61.4 ± 11.7 y (five females/42 males). There were 23 patients in group I (supplemented diet) and 24 patients in the control diet group II. Characteristics of the patients on enrollment were similar for the two groups, reflecting the homogeneity of the patients. There were no significant differences with regard to gender, mean age, body weight, location and stage of tumor (Table 2). Patients had the same percentage preoperative weight loss (group I 5.7% *vs* group II 4.8%; NS) and oral intake (group I 1502±343 cal/day *vs* 1491±323 group II cal/day; NS). Ten patients underwent resection of a tumor located in the oral cavity with unilateral or bilateral neck disection; 37 patients underwent laryngectomy (total or partial) or pharyngo-laryngectomy, with the same distributions of surgery in groups I and II. Duration of enteral nutrition in both groups was similar with an average duration of 22±12 days.

As shown in Table 3, no significant intergroup differences in the trends of the three plasma proteins and lymphocytes were detected. No differences were detected in weight.

Gastrointestinal tolerance (diarrhea) of both formulas was good, with no intergroup differences (17.4% group I and 8.3% group II; NS). There were no dropouts due to intolerance.

During the 3 months after hospital discharge, five patients died; no diferences were detected between groups (13% group I and 8.3% group II; NS). The postoperative infection complications (urinary tract and pneumonia with similar distribution) were similar (nine patients) in both groups (21.7% group I and 16.7% group II; NS). Statistical differences were detected in local complications: fistula diagnosed by X-ray was less frequent in enriched nutrition group (0% group I and 20.8% group II; $P<0.05$); frequency of wound infection was higher in group II, without statistical difference (4.3% group I and 12.5% group II; NS)

The length of postoperative stay was 22.8±11.8 days in the immunonutrition group and 31.2±19.1 days in the control group ($P=0.07$), within the limit of statistical difference.

**Table 2** Patient characteristics

| | *Group I* | *Group II* |
|---|---|---|
| Age (y) | 63.15±12.7 | 59.3±10.5 |
| Men/women | 2/21 | 3/21 |
| Body weight (kg) | 68.2±13 | 67.5±12.2 |
| Body mass index | 26.2±4.7 | 24.1±4.2 |
| Disease stage | | |
| I | 0 | 0 |
| II | 3 | 4 |
| III | 4 | 5 |
| IV | 16 | 15 |
| Diagnosis of disease | | |
| Oral cavity | 5 | 5 |
| Larynx | 18 | 19 |

No statistical differences.

**Table 3** Visceral serum protein and anthropometric parameters

| *Parameters* | *Basal* | *Day 7* | *Day 14* |
|---|---|---|---|
| Albumin (g/dl) | | | |
| Group I | 2.39±0.47 | 3.1±0.68* | 3.98±0.65* |
| Group II | 2.69±0.6 | 2.99±0.53* | 3.91±0.44* |
| Prealbumin (mg/dl) | | | |
| Group I | 13.58±5.7 | 20.58±7.4* | 20.57±5.9* |
| Group II | 13.7±6.2 | 19.8±6.2* | 21.96±5.9* |
| Transferrin (mg/dl) | | | |
| Group I | 146.1±41.6 | 191.1±40.1* | 240.1±51.8* |
| Group II | 150.4±53.5 | 198.1±58.7* | 223.7±35.3* |
| Lymphocytes ($10^3$ µl/mm$^3$) | | | |
| Group I | 1434±522 | 1662±542* | 2096±1168* |
| Group II | 1338±684 | 1552±529* | 2270±841* |
| Weight (kg) | | | |
| Group I | 69.1±13.7 | 68.4±13.4 | 68.8±14.6 |
| Group II | 69.2±12.9 | 67.8±12.6 | 68.5±9.4 |

*$P<0.05$ with basal values.

## Discussion

Malnutrition and immunosuppression were two characteristics of head and neck cancer patients (Riboli *et al*, 1996). Malnutrition is reported in 50% of these patients (Bassett & Dobie, 1990). Malnutrition is due to reduced dietary intake secondary to dysphagia and alcohol consumption (Reilly, 1990); interleukins secreted by the tumor with a catabolic action played a dominant role (Todorov *et al*, 1996). Immunosupression is related to surgery and the immunosuppressive capacity of the tumor (Katz, 1983). For example, Van Bokhorst-de van der Schueren has recently reported that head and neck cancer patients with weight loss exceeding 10% during the 6 months before surgery are at great risk of the occurrence of major complications (Van Bokhorst-de van der Schueren *et al*, 1997).

However, only a few studies have analyzed the immunonutrition formula with arginine or dietary fiber used in our study. Riso *et al* (2000) confirmed that an enteral diet supplemented with arginine in the early postoperative period improved postoperative immunological status and speeded up recovery from the immunodepression following surgical trauma. In the malnourished patients of this study, administration of an enriched formula reduced major postoperative complications and length of postoperative stay significantly. In our study, length of stay was shorter in the enriched formula group, but the difference was not statistically significant; however wound complications (fistula) were also improved in our patients. Snyderman *et al* (1999) with a perioperative nutritional supplementation with an immune-enhancing formula was superior to standard formula in the prevention of postoperative infectious complications. There was no significant difference in wound healing problems or duration of hospitalization. Higher albumin serum was demonstrated in the enriched formula group compared with standard formula. Caparros *et al* (2001) showed in critically ill patients with a diet enriched with arginine and fiber, a decrease in catheter-related sepsis rate. In our study with better nourished patients than those reported in previous studies, no differences were detected in postoperative infection complications, but wound complications were lower and plasma proteins improved with standard and immune-enhancing formula; we do not have a clear explanation for this early improvement in serum proteins in both groups. Another study with an arginine-supplemented formula (Van Bokhorst-de van der Schueren *et al*, 2001) did not show significantly improved nutritional status, reduced immunosuppression, or altered clinical outcome in head and neck cancer patients; however, only 9 days of postoperative tube feeding was used in that study, our patients received an average of 22 days of enteral nutrition.

Arginine stimulates anabolic hormone release, improves survival in gut-derived sepsis and peritonitis by modulating bacterial clearance, and has been demonstrated to enhance natural killer cell cytotoxicity, increase T-cell proliferation, and accelerate wound healing (Reynolds *et al*, 1988). Fiber-supplemented enteral formulas may have a beneficial effect on components of the gut barrier, as well as the gut mucosa, and on bacterial translocation (Cummings, 1983). Insoluble fiber, rich in cellulose and lignin, can exert beneficial effects by increasing fecal mass through water absorption, thereby regulating intestinal transit and decreasing the incidence of constipation and diarrhea. Soluble fiber is degraded by anaerobic colonic flora forming short-chain fatty acids, with a trophic effect on the mucosa of the large bowel.

In conclusion, the enriched formula improves local wound complications in postoperative head and neck cancer patients. Our results suggest that these patients could benefit from an arginine- and fiber-enhanced enteral formula.

## References

Arriaga MA, Johnson JT, Kanel KT & Myers EN (1990): Medical complications in total laryngectomy: incidence and risk factors. *Ann. Otol. Rhinol. Laryngol.* **99**, 611–615.
Bassett MR & Dobie RA (1990): Patterns of nutritional deficiency in head and neck cancer. *Otol. Head Neck Surg.* **91**, 119–125.
Caparros T, Lopez J & Grau T (2001): Early enteral nutrition in critically ill patients with a high protein diet enriched with arginine, fiber and antioxidants compared with a standard high protein diet. The effect on nosocmial infections and outcome. *J. Parent. Enteral Nutr.* **25**, 299–309.
Cummings JH (1983): Fermentation in the human large intestine: evidence and implications for health. *Lancet* 1206–1209.
Daly JM, Reynolds J & Thom A (1998): Immune and metabolic effects of arginine in the surgical patient. *Ann. Surg.* **208**, 521–523.
Di Carlo V, Gianotti L, Balzano G, Zerbi A & Braga M (1999): Complications of pancreatic surgery and the role of perioperative nutrition. *Dig. Surg.* **16**, 320–326.
Gianoti L, Braga M, Fortis C, Soldini L, Vignali A, Clombo S, Radaelli G & Di Carlo V (1999): A prospective, randomized clinical trial on perioperative feeding with an arginine, omega-3 fatty acid, and RNA-enriched enteral diet. Effect on host response and nutritional status. *J. Parent. Enteral Nutr.* **23**, 314–320.
Katz AE (1983): Immunologic stating of patients with carcinoma of the head and neck. *Laryngoscope* **93**, 445–463.
Reilly JJ (1990): Does nutrition management benefit the head and neck cancer patient? *Oncology* **4**, 105–115.
Reynolds JV, Daly JM & Zhang S (1988): Immunomodulatory mechanisms of arginine. *Surgery* **104**, 141–151.
Riboli E, Kaaks R & Esteve J (1996): Nutrition and laryngeal cancer. *Cancer Causes Control* **7**, 147–156.
Riso S, Aluffi P, Brugnani M, Farinetti F, Pia F & Dandrea F (2000): Postoperative enteral immunonutrition in head and neck cancer patients. *Clin. Nutr.* **19**, 407–412.
Snyderman CH, Kachman K, Molseed L, Wagner R, D Amico F, Bumpous J & Rueger R (1999): Reduced postoperative infections with an immune-enhancing nutritional supplement. *Laryngoscope* **109**, 915–921.
Todorov P, Cariuk P, McDevitt T, Coles B, Feaon K & Fisdale M (1996): Charaterization of cancer cachectic factor. *Nature* **379**, 739–742.
Van Bokhorst-de van der Schueren MAE, van Leeuwen PAM, Sauerwein HP, Kuik DJ, Snow GB & Quak JJ (1997): Assessment of malnutrition parameters in head and neck cancer and their relation to postoperative complications. *Head Neck* **19**, 419–425.
Van Bokhorst-de van der Schueren MAE, von Blomberg-van-der Flier BME & Riezebos RK (1998): Differences in immune status between well-nourished and malnourished head and neck cancer patients. *Clin. Nutr.* **17**, 107–111.
Van Bokhorst-de van der Schueren MA, Quak JJ, Von Blomberg-van der Flier ME, Kuik DJ, Langendoen SI, Snow GB, Green CJ & van Leeuwen PAM (2001): Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severely malnourished head and neck cancer patients. *Am. J. Clin. Nutr.* **73**, 323–332.
Wu GH, Zhang YW & Wu ZH (2001): Modulation of postoperative immune and inflammatory response by immune enhancing enteral diet in gastrointestinal cancer patients. *World J. Gastroenterol.* **7**, 357–362.