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 patients1–3

Marian AE van Bokhorst-de van der Schueren, Jasper J Quak, B Mary E von Blomberg-van der Flier, Dirk J Kuik, Sterre I Langendoen, Gordon B Snow, Ceri J Green, and Paul AM van Leeuwen

ABSTRACT
Background: Malnourished head and neck cancer patients are at increased risk of postoperative complications.
Objective: We studied the effect of perioperative, arginine-supplemented nutritional support on nutritional status, immune status, postoperative outcome, and survival in severely malnourished (weight loss >10% of body weight) head and neck cancer patients undergoing major surgery.
Design: Forty-nine patients were randomly assigned to receive 1) no preoperative and standard postoperative tube feeding, 2) standard preoperative and postoperative tube feeding, or 3) arginine-supplemented preoperative and postoperative tube feeding.
Results: Patients in both prefed groups received ≈9 d of preoperative tube feeding, resulting in energy intakes of 110% and 113% of calculated needs (compared with 79% in the control group; P = 0.007). Compared with no preoperative feeding, preoperative enteral nutrition did not significantly improve nutritional status or any of the studied biochemical or immunologic indexes. Major postoperative complications occurred in 53%, 47%, and 59% of patients in study groups 1, 2, and 3 (NS). A trend was seen toward better survival in the arginine-supplemented group (P = 0.15). Secondary analysis showed that survivors had better human leukocyte antigen-DR expression on monocytes (P = 0.05) and higher endotoxin-induced cytokine production (P = 0.010 for tumor necrosis factor α and P = 0.042 for interleukin 6) at the start of the study than did patients who died.
Conclusions: Nine days of preoperative tube feeding, with or without arginine, did not significantly improve nutritional status, reduce the surgery-induced immune suppression, or affect clinical outcome in severely malnourished head and neck cancer patients. Patients supplemented with arginine-enriched nutrition tended to live longer. Some markers of immune function may distinguish patients with good or bad prognoses. Am J Clin Nutr 2001;73:323–32.

KEY WORDS Head and neck cancer, malnutrition, perioperative nutrition, human leukocyte antigen-DR expression, cytokines, postoperative complications, survival

INTRODUCTION
Patients undergoing surgery because of a head and neck malignancy have a 20–50% incidence of postoperative complications (1–4). These complications include major wound infections, fistula, anastomotic leakage, respiratory insufficiency, and septicemia and may lead to not only a prolonged hospital stay but also a poorer prognosis. Several factors may contribute to this morbidity, one of which is malnutrition. Most studies report malnutrition in 35–50% of all head and neck cancer patients, particularly those with squamous cell carcinoma of the oropharyngeal and hypopharyngeal areas (4–7).

In a prospective study at our institute, we used logistic regression to identify a preoperative weight loss of 10% of body weight as a predictive risk factor for major postoperative complications in these patients undergoing major ablative surgery (8). Therefore, the prevention or correction of nutrient depletion might minimize or eliminate malnutrition-related morbidity and mortality. The pooled results of 13 clinical trials suggest that preoperative parenteral nutrition may benefit severely malnourished patients undergoing major cancer surgery by decreasing postoperative complications by ≈10% (9). Consensus has been reached on the duration of preoperative feeding, ie, 10 d (with a minimum of 7 d). Preoperative feeding should result in an improvement in nutritional status as measured by weight gain, with no decrease in blood albumin, and ideally by improved muscle strength (10). Nevertheless, the main perioperative parenteral nutrition trials have not analyzed the response to preoperative nutritional treatment nor have they related changes in nutritional status resulting from preoperative feeding to postoperative outcome (11–13).

Only 3 trials used enteral nutrition to study the effect of preoperative nutritional supplementation on postoperative outcome (12, 14, 15). In these studies, postoperative complication rates

1 From the Department of Dietetics, the Nutrition Support Team, the Department of Otolaryngology/Head and Neck Surgery, the Department of Pathology, and the Department of Surgery, University Hospital Vrije Universiteit, Amsterdam; the Department of Clinical Epidemiology and Biostatistics, Vrije Universiteit, Amsterdam; and the Medical Information Department, Numico Nutritional Healthcare, Zoetermeer, Netherlands.
2 Supported by Numico Research BV, Wageningen, Netherlands
3 Reprints not available. Address correspondence to MAE van Bokhorst-de van der Schueren, University Hospital Vrije Universiteit, Department of Dietetics, PO Box 7057, 1007 MB Amsterdam, Netherlands. E-mail: m.vanbokhorst@azvu.nl.
Received August 31, 1999.
Accepted for publication July 5, 2000.
Before undergoing surgery because their cancer was deemed inoperable (mostly metastatic tumors). The other 49 patients all completed the study. All patients had a histologically proven squamous cell carcinoma of the oral cavity, larynx, oropharynx, or hypopharynx. Patients were excluded from the study if they were well nourished (weight loss <10% of body weight); received other investigational drugs or steroids; had renal insufficiency, hepatic failure, or any genetic immune disorder; or had a confirmed diagnosis of AIDS. The study was approved by the medical ethics committee of the VU Academic Hospital.

Nutrition

After stratification for type of surgery (combined mandibular resection or total laryngectomy) and previous radiotherapy (yes or no), the patients were randomly assigned to 1 of 3 treatment groups according to a computer-generated randomization schedule with an equal probability of assignment to any of the nutritional regimens. Group 1 received no preoperative nutritional support, group 2 received preoperative enteral nutrition with a specially formulated product that closely reflected the current standard of practice (standard formula), and group 3 received preoperative enteral nutrition in which 41% of the casein was replaced by arginine. Nutritional solutions were isoenergetic and isonitrogenous (Table 1). Blinding of patients was possible only in groups 2 and 3. Patients in groups 2 and 3 were given enteral nutrition at home for 7–10 d preoperatively through a nasogastric feeding tube unless medical circumstances necessitated admission to a hospital.

Target intakes were based on estimated energy requirements, calculated as 1.5 × the basal energy expenditure (BEE) estimated by use of Harris and Benedict equations (26) on the basis of actual weight. Tube-fed patients (groups 2 and 3) received their complete nutritional needs by enteral feeding, but were allowed to eat in addition to tube feeding if wanted. Patients in group 1 were stimulated to continue their usual oral diet preoperatively; no additional supplements were prescribed. Patients were requested to record all nutritional intake in a diary. In addition to recruitment, patients had at least one telephone contact with the research dietician during the preoperative period.

Postoperatively, all patients received tube feeding (1.5 × BEE) starting on the first postoperative day until an X-ray conducted to assess swallowing ability performed 10 d after surgery showed no leakage from anastomoses (repeated “swallowing X-rays” were scheduled if anastomotic leakage occurred). Postoperatively, groups 1 and 2 were given the so-called standard formula, whereas group 3 received the arginine-supplemented formula.

Patient monitoring

Patient monitoring included nutritional assessment, immunologic evaluation, and assessment of clinical outcome and survival at the following time points: at recruitment into the study, 1 d preoperatively, 1 d postoperatively, 4 d postoperatively, 7 d postoperatively, and on the day of discharge. Follow-up time for survival was ≥16 mo.

Nutritional assessment

Anthropometric and biochemical indexes were measured to assess nutritional status. Anthropometric measurements included body weight, body composition, upper midarm circumference, skinfold thickness, and muscle function. Body composition (body fat and lean body mass) was computed from results of
bioelectrical impedance analysis (RJL Systems Inc, Clinton Township, MI) with an age-specific computer program (BODYGRAM; RJL Systems Inc, Detroit). Skinfold thickness (biceps, triceps, subscapular, and suprailiac) and midarm muscle circumference were used to calculate fat and lean body mass (27). Muscle function tests consisted of measurements of hand grip strength with a dynamometer (Jamar Dynamometer; Somow Engineering Co, Los Angeles), which is reported as the most accurate method of measuring grip strength under standardized conditions (28, 29). The second handle position was used as the standard to compare patients (29). Biochemical assessment included measurement of serum albumin and electrolytes and liver and kidney function tests.

**Immunologic evaluation**

The following immune variables were measured in fresh (<6 h old) heparin-treated venous blood after erythrocyte lysis of whole blood samples (Q-prep; the Coulter Corporation, Miami): the absolute numbers of leucocytes and lymphocytes, the total lymphocyte count, and the percentages of monocytes (CD14+), pan T lymphocytes (CD3+), T helper lymphocytes (CD4+), T suppressor lymphocytes (CD8+), B lymphocytes (CD19+), natural killer (NK) cells (CD16/CD56+/CD3−), and NK-like T cells (CD16/CD56+/CD3+). In addition, human leukocyte antigen-DR (HLA-DR) expression in CD14+ cells was evaluated by FACS analysis (FACStar Plus; Becton Dickinson, San Jose, CA) and expressed as the ratio of fluorescence intensity (mean fluorescence and peak channel) with anti-HLA-DR–fluorescein isothiocyanate to that without. All monoclonal antibodies were purchased from Becton Dickinson.

Furthermore, the ex vivo production of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) in whole blood samples was measured after stimulation of the samples with lipopolysaccharide (LPS; Difco Laboratories, Detroit) in final concentrations of 0, 0.01, 1, and 100 μg LPS/L. Samples were incubated for 4 h (at 37°C, 5% CO2) and production of IL-6 and TNF-α (ng/L) was measured in the supernates by means of a cytokine-specific enzyme-linked immunosorbent assay (CLB, Amsterdam).

**Clinical outcome**

Assessment of outcome was based on the perioperative use of blood, blood products, and antibiotics; the occurrence of postoperative complications; the date of normal swallowing as confirmed by X-ray (indicating that the patients could begin drinking fluids); and the date of discharge from the hospital. Postoperative complications were categorized as absent, minor (including minor wound infections, redness and induration of the wound, pulmonary infections, and urinary tract infections), or major (including wound infections requiring surgical drainage, orocutaneous or pharyngocutaneous fistula, flap failure, radiologic signs of anastomotic leakage, respiratory insufficiency, cardiac failure, and septic shock) (8).

**Survival**

On 1 April 1999, after a follow-up period of ≥16 mo, the records of all patients were studied to assess survival and cause of death. No patient was lost to follow-up. Survival analysis was performed both for overall survival and for disease-specific survival. Disease-related death was defined as in-hospital postoperative death within 30 d of the last surgery, death from recurrent tumor, or death from a second primary tumor.

**Statistical procedures**

From earlier studies it was known that 60% of malnourished head and neck cancer patients have major postoperative complications, whereas this figure is 20% in well-nourished patients (8). To reduce the percentage of major postoperative complications from 60% to 30% in the nutrition intervention groups, the sample size was calculated to be 39 patients per study group with 80% power and 5% significance. Because patient recruitment was much slower than expected, however, recruitment ended on 31 December 1997 for financial reasons.

One-way analysis of variance (ANOVA) was used to compare continuous variables. Chi-square tests were used to compare discrete variables. A two-factor repeated-measures ANOVA was applied to analyze group and time interactions. Survival curves for all patients and for subgroups were made according to the methods of Kaplan and Meier (30). Immunologic tests with different baseline values at the start of the study (because of individual biological spread) were set at a 100% starting point and calculated from there. The overall pooled CV (ie, a time-point-corrected intrindivid-ual CV) was computed for the cytokine production data. Calculations were made with SPSS (SPSS Inc, Chicago) and BMDP (BMDP Statistical Software, Los Angeles) computer software. All P values ≤0.05 were considered to indicate statistical significance. Results are presented as means ± SDs, unless stated otherwise.

**RESULTS**

Seventeen patients were allocated to group 1, 15 to group 2, and 17 to group 3. Patient characteristics are described in Table 2. The groups did not differ significantly in age, tumor stage, tumor localization, comorbidity, or weight loss. Group 2 included more women than did the other 2 groups, but this difference was not significant. The ratio between combined mandibular resections and total laryngectomies and the type of reconstructive surgery (primary closure, pectoralis major flap reconstruction, or free flap reconstruction) was not significantly different between the

**Table 2**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>55 ± 10</td>
<td>60 ± 8</td>
<td>59 ± 12</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>IVa</td>
<td>11</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>IVb</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent tumor</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Not staged</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tumor localization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Larynx</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Comorbidity (yes/no)</td>
<td>2/15</td>
<td>3/12</td>
<td>4/12</td>
</tr>
<tr>
<td>Preoperative weight loss (%)</td>
<td>15.4 ± 5.9</td>
<td>17.1 ± 7.2</td>
<td>12.8 ± 5.1</td>
</tr>
</tbody>
</table>

1 Group 1, no preoperative nutritional support and standard postoperative tube feeding; Group 2, standard preoperative and postoperative tube feeding; Group 3, arginine-supplemented preoperative and postoperative tube feeding. There were no significant differences between groups.

2 CV ± SD.
3 groups. For all patients, the mean duration of surgery was 8.6 ± 3.1 h and the mean recorded blood loss during surgery was 1.525 ± 1.037 L. For neither index were significant differences between groups noted.

In the preoperative period, patients in groups 2 and 3 reached 110% and 113% of their estimated energy requirements, respectively, whereas patients in group 1 reached only 79% (P = 0.007). Preoperative tube feeding was provided for 8.8 ± 8.6 d (group 2) and 8.6 ± 1.4 d (group 3). Energy intake in these groups was mostly from tube feeding; only 10% (group 2) to 15% (group 3) of total intake came from oral food intake.

**Anthropometric measurements at baseline and after the preoperative intervention**

<table>
<thead>
<tr>
<th>Baseline</th>
<th></th>
<th></th>
<th></th>
<th>Mean change after intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.8 ± 4.4</td>
<td>55.3 ± 8.1</td>
<td>61.6 ± 8.5</td>
<td>0.039</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>12.2 ± 8.7</td>
<td>10.5 ± 6.7</td>
<td>13.0 ± 5.8</td>
<td>0.61</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>42.1 ± 16.8</td>
<td>36.3 ± 17.0</td>
<td>47.5 ± 6.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>27.9 ± 9.5</td>
<td>26.7 ± 9.5</td>
<td>33.6 ± 10.9</td>
<td>0.07</td>
</tr>
<tr>
<td>Left</td>
<td>27.9 ± 13.9</td>
<td>26.4 ± 11.0</td>
<td>29.2 ± 14.6</td>
<td>0.84</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>37.3 ± 4.0</td>
<td>32.9 ± 6.4</td>
<td>35.9 ± 4.0</td>
<td>0.047</td>
</tr>
</tbody>
</table>

1 Group 1, no preoperative nutritional support and standard postoperative tube feeding; group 2, standard preoperative and postoperative tube feeding; group 3, arginine-supplemented preoperative and postoperative tube feeding.

2 There were no significant time × group interactions and no significant mean changes by time (two-factor repeated-measures ANOVA).

3 When calculated for men and women separately, no significant differences were found.

3. Baseline weight was lower in group 1 than in the other groups. This may have been because of the larger number of women in this group. When women and men were compared separately, baseline weights for women and baseline weights for men were not significantly different between groups. No significant changes in nutritional status were noted between the 3 groups as a result of nutritional intervention.

**Nutritional assessment**

**Anthropometry**

The results of the most important anthropometric measurements before and after the period of preoperative nutritional intervention are shown in Table 3. Baseline weight was lower in group 2 than in the other groups. This may have been because of the larger number of women in this group. When women and men were compared separately, baseline weights for women and baseline weights for men were not significantly different between groups. No significant changes in nutritional status were noted between the 3 groups as a result of nutritional intervention.

**Biochemistry**

Serum albumin concentrations differed significantly between groups at the start of the study (Table 3). In the week of preoperative intervention, mean albumin concentrations decreased in group 1 but did not change significantly in groups 2 and 3 (P = 0.055 for the time × group interaction). Postoperatively, albumin concentrations decreased as a result of surgery, but no significant differences were noted between groups.

**Immunologic assessment**

The numbers of lymphocytes and T lymphocytes (CD3+) and the percentage of T suppressor lymphocytes (CD8+) differed significantly between groups at the start of the study. Therefore, these indexes were set at 100% at the start of the study and differences were measured from that point on. Although at some time points changes in immunologic indexes were significantly different between groups for leukocytes, monocytes, lymphocytes, and T helper cells, these differences were inconsistent and overall patterns were much the same.

Patients in all 3 groups showed profound immunologic disturbances in response to surgery: there was a clear drop in total lymphocyte count, caused particularly by a decrease in the number of T helper lymphocytes (CD4+); a strong reduction in HLA-DR expression on monocytes (Figure 1); and an increase in the number of leukocytes. The HLA-DR expression on monocytes, which is known to be a sensitive index of the severity of surgery-induced immune suppression, was comparable between groups at all time points.

The effect of surgery on endotoxin-induced cytokine production was also clear-cut. TNF-α and IL-6 production increased in the absence of or with low amounts (0.01 g/L) of LPS. In contrast, when stimulated with 1 or 100 g LPS/L, cytokine production dropped sharply after surgery. Because the patterns for TNF-α and IL-6 were identical, only data for IL-6 production are shown in Figure 2.

**Clinical outcome**

Nine of 17 patients (53%) in group 1, 7 of 15 (47%) in group 2, and 10 of 17 (59%) in group 3 had major postoperative complications. The type and severity of the complications (fistula formation, wound and flap complications, arterial bleeding, and respiratory insufficiency) did not differ significantly between groups. Three patients died as a result of postoperative complications: 1 in group 2 and 2 in group 3. Three patients in group 1 and 5 patients each in groups 2 and 3 never resumed swallowing. No significant differences were found in the time to resumption of swallowing, although all patients in group 3 who did resume swallowing did so within 40 d, whereas the scatter in groups 1 and 2 was greater. The same pattern was seen for time until discharge from the hospital; this was 41 ± 32 d for patients in group 1, 46 ± 30 d for patients in group 2, and 31 ± 23 d for patients in group 3 (NS). No significant differences between groups were found in the postoperative use of blood products or antibiotics or in any of the other recorded clinical indexes.

**Survival**

At the time of survival analysis, 32 patients had died. Overall survival was 35%: 42% for men and 22% for women (NS). The main cause of death was recurrent disease (local-regional
recurrence alone, \( n = 9 \); local-regional recurrence combined with distant metastases, a second primary tumor, or both, \( n = 7 \); and distant metastases only, \( n = 2 \). Four patients died of a second primary tumor. Three patients died within the first 30 d after surgery (in-hospital death).

Seven patients were excluded from the disease-specific survival analysis (all men). These patients died of causes other than cancer (pulmonary insufficiency, \( n = 2 \); pulmonary embolism, \( n = 1 \); gastric hemorrhage, \( n = 1 \); stroke, \( n = 1 \); suicide, \( n = 1 \); and unknown, \( n = 1 \)). Disease-specific survival was 49%: 64% for men and 22% for women \((P = 0.045)\). No significant difference in survival was noted between the 3 groups, although there was a trend toward a better survival for patients in the arginine-supplemented group \((\text{Figure 3}; P = 0.15)\).

In a retrospective comparison of survivors with patients who died, we found that survivors had a lower preoperative weight loss (12.4%) than did patients who died (16.5%; \( P = 0.034 \)). In addition, survivors had better HLA-DR expression on monocytes (mean fluorescence, \( P = 0.050 \)) and a higher capacity to produce cytokines \( [\text{both IL-6} (P = 0.042) \text{ and TNF-\alpha} (P = 0.010)] \) on stimulation with high doses of LPS \((100 \, \mu\text{g/L})\). This pattern was seen at the start of the study and continued throughout the whole study period. No significant differences were found within groups of survivors and groups of patients who died, as shown for HLA-DR expression in \text{Figure 4}.

**DISCUSSION**

The results of this study failed to support the hypothesis that preoperative feeding, either with or without arginine supplementation, improves clinical outcome, intermediate markers of immune function, or nutritional status compared with ad libitum oral food intake. No conclusions can be made about the value of perioperative feeding per se because all 3 groups of patients received tube feeding postoperatively.

**Nutrition**

The rationale for preoperative feeding in this study was the well-described link between disease-related malnutrition and poor clinical outcome. However, this association does not imply cause and effect; disease-related malnutrition may simply be a marker of the severity of disease. If malnutrition occurs as a result of altered metabolism \((31)\) and not purely as a result of diminished intake, patients are less likely to respond to nutritional therapy. The results of this study lend some support to this hypothesis.

In this study, the target group was selected as those thought most likely to benefit from preoperative feeding, ie, those who were severely depleted. This decision was based on other work in which the most severely depleted were the only ones who showed benefit of perioperative parenteral nutrition \((11)\). However, in that study, total parenteral nutrition was used and the morbidity associated with this may have been sufficient to obscure benefit in the less severely malnourished patients; furthermore, those patients would not currently be regarded as candidates for total parenteral nutrition because enteral nutrition is the feeding method of first choice.

Three previous studies compared preoperative enteral nutrition with routine practice \((\text{Table 4})\). Not all patients in these studies were malnourished, head and neck cancer patients were not included, and study results were equivocal. Moreover, the positive results of 2 of these studies \((14, 15)\) can be countered by criticism of the statistical handling of data \((16)\). The third study did not show better results for patients treated with preoperative enteral nutrition than for those treated by routine practice \((12)\).

Furthermore, the nutritional intervention in the present study should be discussed. First, we expected the control group to have a low food intake because of the obstruction and dysphagia caused by the localization of the tumor. To our surprise, control patients consumed \( \approx 80\% \) of their estimated requirements \( (\text{compared with} \pm 110\% \text{ in both enterally fed groups}) \). It may thus be hypothesized that although the differences in nutrient intake between the 3 intervention groups were indeed statistically significant, they were too small to be clinically relevant and could explain the results as described.

Second, nutritional intervention may not have been aggressive enough. Complication rates were similar to those described previously \((8)\) and the lack of difference in results was thus not due to an improvement in all 3 groups. One explanation is that...
nutritional status was not ameliorated by 9 d of preoperative nutrition. This is in line with a study by Bruning et al (32) suggesting that (postoperative) energy requirements for head and neck cancer patients are much higher than generally accepted. Perhaps these patients are too catabolic or severely ill to benefit from standard tube feeding regimens. This raises questions about whether feeding of any type would be able to bring about an anabolic response (ie, would incorporation of other ingredients or different ratios of macronutrients have an influence?).

A final consideration is that the length of nutritional support was not sufficient for repletion of these extremely malnourished patients. Seven to 10 d of preoperative nutrition has become the gold standard for patients with an approximate weight loss of 10% of body weight (9, 10). It may be that a longer period is necessary for patients experiencing greater weight loss, that nutritional therapy is not useful at all for this category of patients, or that a more aggressive form of nutritional therapy is necessary for patients undergoing massive surgery. The results of our study agree with the negative results of nutrition intervention studies in patients undergoing major surgery of the upper gastrointestinal tract (33, 34), but are in contrast with the positive results found in patients undergoing predominantly less invasive surgery of the lower gastrointestinal tract (35, 36). This suggests that the severity of the trauma is possibly of more importance than is the severity of depletion.

There is now some evidence that a positive response to nutritional therapy is a predictor of clinical outcome. In patients with chronic obstructive pulmonary disease or HIV it was shown that prognosis improved only in those who responded to nutritional therapy (37, 38). This raises new questions: how will we be able to identify in advance malnourished patients who are likely to respond to nutritional support? How long a period of nutrition therapy is needed for a positive response?

Taking all of this into consideration, we conclude that more work is required to determine whether earlier, more aggressive, or differently composed nutritional support may be more effective in extremely malnourished patients undergoing a major catabolic event. In addition, the challenge exists to find a variable that will distinguish patients who will benefit from nutritional support from those who will not.
Immunology

Malnutrition, head and neck cancer, and surgery are all associated with impaired immune function, especially with regard to cellular immunity (39–41). Specific nutrients have been reported to improve immune responsiveness after experimental injuries (42–44). Arginine is one such nutrient that is expected to be of benefit via its purported role in stimulating components of immune function, nitrogen balance, and wound healing. Supplementation with arginine (30 g/d) is associated with increased lymphocyte blastogenic responses to mitogens and decreased numbers and percentages of CD8+ cells in healthy human volunteers (19). In contrast, in surgical and in gastric cancer patients, the same amount of arginine supplementation does not induce changes in phenotypic subsets in lymphocytes, suggesting that immune function in these patients is more an intrinsic lymphocyte defect than a component of impaired nutritional status (45,46). Studies investigating the combined effects of arginine, n−3 fatty acids, and RNA after surgery often showed improved immune reactions, but results regarding clinical outcome were equivocal (23–25,33). Other reports contradict the immune-modulating effects of immune-enhancing enteral formulas and did not find alterations in lymphocyte or monocyte functions (47,48). However, no study tested the use of arginine as the sole variable in a preoperative setting.

In this study we were unable to show any noticeable immunologic differences between the arginine-supplemented group and the other 2 groups. In all 3 groups, surgery induced the same profound immunologic response, characterized by increased leukocytes, decreased lymphocytes, and severely depressed HLA-DR expression on monocytes. The degree of immunologic impairment induced by trauma or surgery is assumed to be related to the severity of tissue injury (49). Therefore, in our study, the extent of the trauma might have masked minor improvements in immune function. The diminished ability of monocytes to express HLA-DR antigens and the delayed return to normal levels is correlated directly with both infection and death (50–53). This agrees with the relatively high postoperative morbidity (>50%) in our patient groups.

The increased production of cytokines on stimulation with no or low concentrations of LPS on day 1 postoperatively agrees with the literature (31). With higher doses of LPS, this reaction was not seen (endotoxin tolerance). This state of hypoinflammation was described in patients with sepsis and trauma as well and is, as is HLA-DR, thought to depend on the extent of trauma and to represent an autoprotective mechanism of the host against the detrimental effects of overwhelming cytokinemia. However, the reaction can also be detrimental for the host because proinflammatory cytokines are required to orchestrate the inflammatory response and to avoid immunodeficiency (54–56).

Secondary analysis showed that survivors had a better ability to express HLA-DR on monocytes and to produce cytokines on stimulation with the highest dose of LPS (100 ng/L) than did those who died. Our findings indicate that the cells of patients who later died underwent a more severe downward catabolic cycle and showed greater signs of exhaustion than did the cells of patients who survived. These discoveries suggest that there are indeed markers that distinguish patients who are already far in the catabolic process from patients with less severe involvement. The results underline the prognostic value of these markers and suggest that endotoxin tolerance is, in this case, a bad omen.

Survival

With respect to the trend toward better survival in the arginine-supplemented group, it can only be hypothesized how short-term arginine supplementation may influence long-term survival. Recent reports in the literature suggest that perioperative restoration of the immune system by l-arginine improves immune function (45, 57, 58), thus reducing tumor outgrowth and thereby enhancing future survival. Possibly, a parallel may
FIGURE 4. Human leukocyte antigen-DR (HLA-DR) expression in severely malnourished head and neck cancer patients who survived or died after surgery. Data are presented for all patients; for all survivors, according to nutrition intervention group; and for all who died, according to nutrition intervention group. Group 1, no preoperative nutritional support and standard postoperative tube feeding; group 2, standard preoperative and postoperative tube feeding; group 3, arginine-supplemented preoperative and postoperative tube feeding. Survivors: all, n = 17; group 1, n = 6; group 2, n = 2; group 3, n = 9. Those who died: all, n = 32; group 1, n = 11; group 2, n = 13; group 3, n = 8. *Significantly different from those who died, P = 0.050.
be drawn from the long-term effects of exogenous supplementation with glutamine: it has been suggested that a benefit would be seen in the prevention of late deaths if supply was a limiting factor and that the time scale for measuring benefits of nutritional support should be extended. Deaths occurring early after surgery are less likely to be prevented by nutritional intervention because they are possibly related more to the severity of the illness than to any depletion in nutritional reserve (59, 60).

A final remark concerns the number of patients included in the trial. Each study group consisted of 15–17 patients; although these numbers are rather small they are typical of a single-center clinical study. Therefore, trends could be important. The most prominent trend was seen in survival, in favor of the arginine-supplemented group. For future research, we performed a new power analysis to estimate the numbers of patients needed for a follow-up trial comparing arginine-supplemented nutrition with a control. We would need 40 patients per treatment for a survival analysis at 3 y, with \( \alpha = 0.05 \) and a power of 80%. At 2 y, with \( \alpha = 0.05 \) and a power of 95%, we would need 129 patients per study group.

**Conclusion**

This study failed to show a beneficial effect of 9 d of preoperative feeding in this cohort of severely depleted patients with head and neck cancer undergoing extensive surgery. Addition of arginine, an ingredient that was expected to have an additional positive effect on immune function, had no influence. This may have been due to an inadequate period of feeding, an inappropriate choice of formula, or, in part, the modest increase in nutrient intake between the 2 tube-fed groups and the group fed an ad libitum diet preoperatively. Another explanation may be that these patients were simply too depleted to benefit from nutritional support at this late stage of their illness or were undergoing too great a surgical stress for this short-term intervention to have an effect. What the results do suggest is that, perhaps contrary to current opinion, the most malnourished patients may be the least likely to benefit from short-term nutritional intervention. Further research using earlier, aggressive preoperative nutritional support in patients with less severe depletion is necessary to explore this hypothesis.

### REFERENCES