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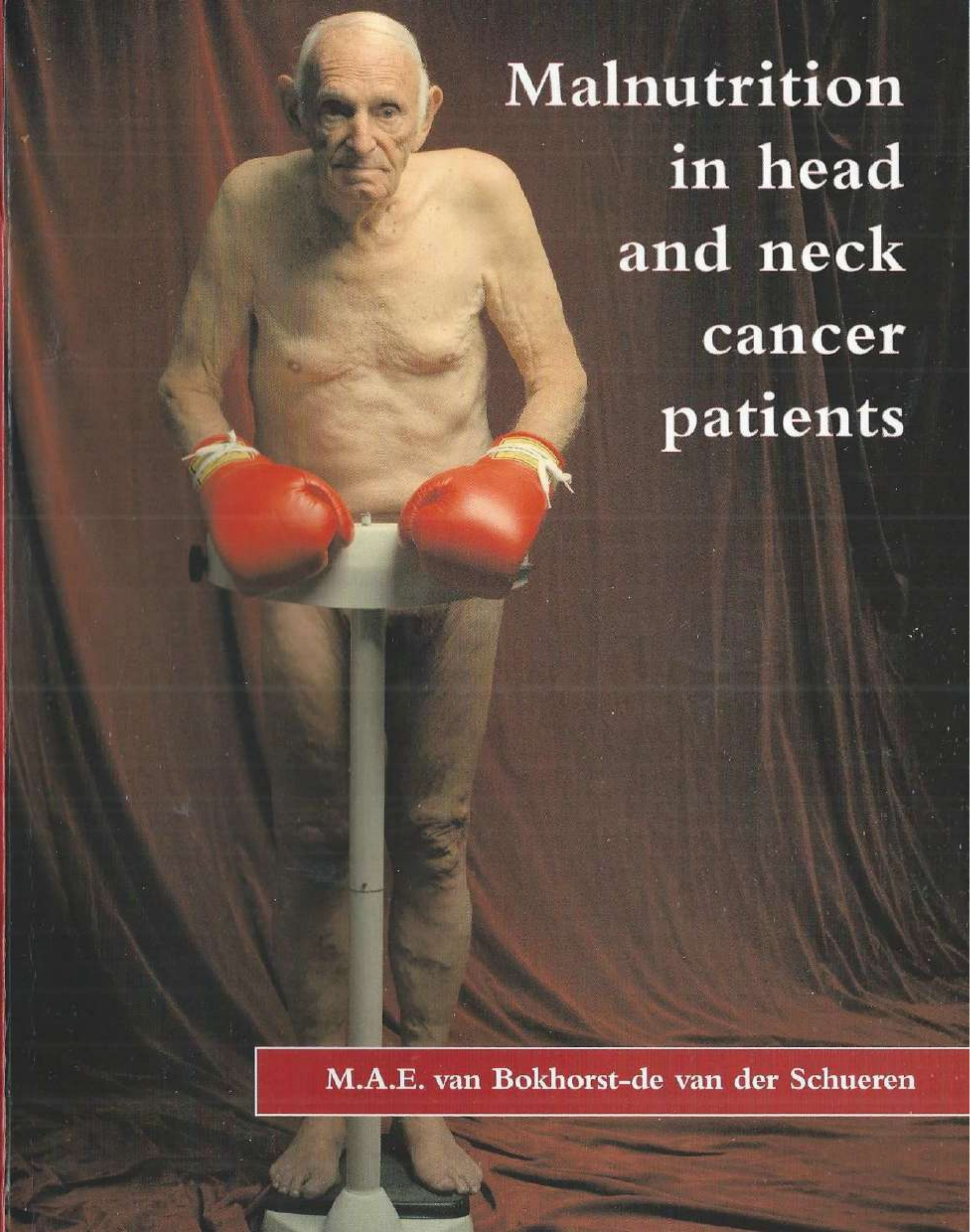
M.A.E. van Bokhorst-de van der Schueren



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MALNUTRITION IN HEAD AND NECK CANCER PATIENTS

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dr. P.A.M. van Leeuwen

Voor Gerbrand,
Querijn en Julie

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Introduction and outline of the thesis

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Introduction

Even in hospital setting malnutrition, particularly in patients with head and neck cancer, is an underestimated problem. In this thesis, first a brief review is given of literature about items related to malnutrition of (head and neck) cancer patients, which literature has left us with some unanswered questions. These questions have inspired us to start this project, the outline of which is described in the second part of this chapter.

Review from the literature

Nutritional status

Malnutrition

Although malnutrition is usually associated with development countries, it occurs in Western hemisphere as well. It is, in these countries, considered to be only a minor problem compared with that of overweight. In hospital settings however, there is growing awareness that malnutrition (i.e. weight loss, loss of lean body mass, depletion of fat mass or low levels of serum proteins) may play an important role in the course of the treatment of patients.

Several studies have reported malnutrition to occur in 25-45% of patients (both surgical and medical) on admission to hospital and to increase to over 60% during admission[1-6]. The pathogenesis of disease-related malnutrition is multifactorial, but reduced food intake due to loss of appetite, episodes of fasting, pain on eating, swallowing difficulties and inability to eat independently may all play a role of importance. Moreover, there may be a disturbance in energy balance depending on a number of regulatory substances including cytokines, glucocorticoids, catecholamines, insulin and insulin-like growth factors[7]. Changes in nutritional status vary with the type of tumour and tumour progression; while in one type of cancer, obstruction of the digestive tract may be the main course of malnutriton, in another type alterations in metabolism may account for the deterioration of nutritional status. Numerous studies have shown that disease-related malnutrition leads to diminished tolerance of treatment, a decreased perception of quality of life, increased risk of complications and even increased mortality. Additionally, it leads to an increased length of hospital stay and rise in costs[6,8-13].

Cachexia

Cancer cachexia is a complex symptom consisting of ongoing anorexia, progressive weight loss, muscle wasting, general weakness and organ dysfunction[14,15]. In 1932, Warren was the first person to describe that death in 22% of cancer patients can be attributed to cachexia[16]. Although its aetiology is not completely understood, anorexia, tumour localisation, cancer therapy, tumour needs and changes in metabolism are known to be of influence[17]. The condition of the cachectic patient differs from "simple" malnutrition due to fasting or starvation because host intermediary metabolism (carbohydrate, lipid and protein metabolism) is abnormal limiting the success of nutritional therapy[18,19].

Nutritional assessment

There is no general agreement in medicine about assessment of the nutritional status of a patient. A variety of nutritional parameters are frequently used to assess nutritional status including plasma proteins (total protein, albumin, pre-albumin, gamma globulins, plasma transferrin), anthropometric measurements (height, weight, skinfold thicknesses), body composition measurements (bioelectrical impedance analysis), and immune function parameters (total lymphocyte count, delayed cutaneous hypersensitivity skin tests). Most of these parameters are altered both by disease and by insufficient food intake. It always remains unclear whether abnormal values are a result of the disease, the diminished nutritional status or the combination of both.

So far, no single nutritional measure is regarded as the best parameter to identify patients at nutritional risk. Therefore, nutritional risk indices combining nutritional parameters have been developed in order to get a reliable picture of patients' nutritional status[20-22].

Head and neck cancer

Incidence, treatment and prognosis

Head and neck squamous cell carcinoma (HNSSC) accounts for approximately 90% of all head and neck tumours. During 1994 approximately 43.000 Americans developed head and neck cancer and 11.500 died from it. Worldwide more than 500.000 new cases are projected annually, and the incidence is rising. In the Netherlands the incidence of HNSCC is about 14 per 100.000 persons a year. In 1995, alsmost 2.000 individuals developed HNSCC and approximately 600 died from it[23]. About one-third of the HNSCC patients present with early stage (I and II) disease, while two-third presents with locoregionally advanced disease (stage III and IV)[24]. Early stage HNSCC can be cured with surgery or radiotherapy alone in the great majority of cases. Patients with advanced stages of disease are mostly treated with a combination of surgery and radiotherapy. Nodal stage and failure to eradicate the disease above the clavicles are traditionally recognized as the most important prognostic factors in these patients[25-28].

Nutritional status

Head and neck cancer patients are among the most malnourished of cancer patients owing to their poor dietary practices, location of tumours in the upper aerodigestive tract, and frequent presentation at a late stage of tumour[29-32]. Malnutrition has been reported in 30-50% of patients with head and neck malignancies, particularly the squamous cell carcinomas of the oropharyngeal and hypopharyngeal area[29,31,33]. The apparent nutritional depletion in these patients is thought to reduce the tolerance to treatment[31,33,34].

Immune function

Many studies have described impaired immune function in head and neck cancer patients, which is thought do be due to various circulating suppressive factors such as suppressor T-cells, suppressor macrophages and to various serum factors including excessive prostaglandin synthesis by the tumour[35]. Several factors are known to cause decreased immune function in head and neck cancer: the malignancy itself, malnutrition, a history of alcohol and tobacco abuse and the surgical trauma[36].

Immunologic derangements may, in turn, have consequences for susceptibility to infection.

Several studies have described a relation between impaired immunocompetence and prognosis in head and neck cancer patients[36-41]. The best documented correlation between immunocompetence and prognosis in head and neck cancer patients has been the evaluation of delayed hypersensitivity[36]. However, the clinical relevance of skin-testing still needs to be determined, because the cause of depressed delayed hypersensitivity is multifactorial, especially in cancer patients[42,43]. While the older studies revealed a depression in number and function of T-cells and B-cells[42-46], more recent investigations have turned to evaluating more specific cellular immune function[47-49].

Since the underlying mechanisms of the observed immunosuppression in head and neck cancer are thought to be multifactorial, it remains to be explored what the contribution of malnutrition may be.

HLA-DR

Class II major histocompatibility antigens, such as HLA-DR, play a crucial role in mounting antigen specific immune responses to micro-organisms and tumour antigens[50]. Several authors have suggested that an imbalance between pro-inflammatory and anti-inflammatory responses can result in immune disturbance, which may present as a decrease in HLA-DR expression and a diminished ability to produce pro-inflammatory cytokines[51-53]. Elderly patients and patients with cancer are known to be at increased risk for this imbalance[51].
Earlier studies found the HLA-DR expression on monocytes to be impaired both in malnutrition and in head and neck cancer[40,54]. In patients with sepsis, reduced HLA-DR expression has been associated with a much higher mortality[55]. Moreover, a diminished ability of monocytes to express HLA-DR has previously been shown to correlate with infection and death in trauma patients[56,57].

Cytokines

Cytokines are hormone-like peptides, which are critical determinants of the response to injury and infection. They influence the production and function of immune cells, the cardiovascular and the metabolic system. In human studies, increased cytokine levels and decreased cytokine production in response to stimulation with endotoxin have been reported in (cancer-)cachexia in general[58,59] and in head and neck cancer patients specifically[60-63]. In malnourished head and neck cancer patients, improving body weight by use of megestrol acetate, an appetite stimulator, lowered cytokine levels, thus suggesting a relation between nutritional status and cytokine levels[60].

Surgery related immune suppression

Numerous clinical and experimental studies have documented that surgery and other forms of trauma alter all aspects of the immune response. In this respect the protection of patients' immunity around surgery deserves special attention. Postoperative changes in the systemic immune respons are proportional to the degree of surgical trauma and subsequent immune suppression may be implicated in the development of postoperative complications and sepsis. Immunosuppression induced by surgery may also predispose to tumour metastases[64]. In patients undergoing surgery for colorectal cancer, circulating tumour cells have been demonstrated in 36% of patients[65]. However, this has never been shown in head and neck cancer patients.

The surgery-induced immunosuppression is depending on the degree of the trauma[66]. HLA-DR expression on monocytes has been found to serve as a parameter for this immunosupression. Studies have shown a significant reduction of HLA-DR expression one day after conventional surgery, but not after laparoscopic[67,68]. In addition, it was found that laparoscopic surgery, in contrast to conventional surgery, resulted in a preservation of the plasma opsonic capacity and thereby the ability of polymorphonuclear leukocytes to phagocytose bacteria. This is thought to play a role in the prevention of postoperative infectious complications[69].
New treatment modalities to decrease immunosuppression are now being investigated, including nutritional intervention and pre-operative treatment with GM-CSF. Enteral nutrition containing a mixture of immunonutrients has been shown to improve immune, metabolic and clinical outcomes in GI cancer patients[70]. In a recent study with colorectal cancer patients it was shown that the surgery-induced depression of HLA-DR expression on monocytes could be reduced by pre-operative treatment with GM-CSF[71]. Until now, no such studies have been performed in head and neck cancer patients.
It is not clear how surgery-induced immune depression is originated. Glutamine plasma levels and/or fluxes may play a role. Low plasma levels of glutamine have been demonstrated after major surgery, while normal levels were seen after minor surgery[72]. Recently it was shown that very low levels of glutamine after extensive trauma could be restored by a glutamine-enriched diet[73,74]. A possible explanation may be found in the enhanced endogenous production of arginine; it has been demonstrated that glutamine-enriched diets increase arginine production in the kidney[75].
It is thus suggested that the immunosuppression caused by surgery may be modulated by peri-operative mediators such as nutrients (like arginine or glutamine) or growth factors.

Nutritional intervention

Peri-operative nutrition

In view of the known associations between poor nutritional status and clinical outcome[6,8-13], it has been suggested that pre-operative feeding in malnourished patients in general can help to improve postoperative outcome. A number of studies have examined the role of pre-operative nutrition. The pooled results from 13 clinical trials suggest that pre-operative parenteral nutrition may benefit the severely malnourished patient undergoing major surgery by decreasing postoperative complications by approximately

10 percent[76]. The optimal duration of pre-operative feeding is proposed to be 10 days (with a minimum of 7 days). This should achieve an improvement in nutritional state represented by weight gain, with no fall in blood albumin, and ideally by improved muscle strength[77].
Although only 3 trials have investigated the role of pre-operative enteral nutrition support, this proved to be as effective or even more effective than parenteral repletion[10,78,79]. Until now, the benefit of pre-operative nutrition has not been established for head and neck cancer patients specifically. Furthermore there is no available evidence to suggest that, as far as peri-operative nutritional support is concerned, the parenteral route of administration is in any way superior to the enteral route[80].

Arginine

Several trials have studied the peri-operative administration of immunonutrients in order to improve patients' outcome. In most of these studies, a combination of immunonutrients was applied, arginine being one of them.
Arginine is an amino acid, best known as an intermediate in the urea cycle. It is generally considered nonessential, since under normal conditions requirements for the amino acid are met through tissue synthesis[81]. However, it is suggested that additional arginine may be required in stressed states such as trauma, burns or sepsis[82]. It plays an important role in T- and B-cell immunity as well as the production of nitric oxide. Dietary supplementation with arginine has been associated with positive effects on immune function and reparative collagen synthesis[82], which might make it a useful nutrient in the peri-operative treatment of head and neck cancer patients, whom are known to be susceptible for both immune disturbances and postoperative wound infections. The exact mechanism through which arginine may exert its immunostimulatory properties has never been defined, although polyamines and hormonal pathways are thought to play a role[70, 83-87].
The majority of the studies that applied a mixture of immunonutrients containing arginine showed improved immune reactions, but it still remains unclear whether the metabolic advantages of the enriched formulas also translate into improved clinical outcome[70,86-90]. Other reports contradict the immune-modulating effects of immune-enhancing enteral formulas and did not find alterations in lymphocyte and/or monocyte functions[91,92]. No study has tested the use of arginine as the sole variable in a prospective pre-operative setting.

Quality of life

The treatment of patients with advanced head and neck cancer consists of extensive surgery, often in combination with adjuvant radiotherapy. For patients this treatment not only brings them face to face with life-threatening illness, they also have to undergo a treatment that may lead to varying changes in physical appearance and possible loss of swallowing function and ability to talk or communicate. In parallel with improvements in technical procedures and a longer life expectancy, more attention has been given to assessment of quality of life in head and neck cancer patients[93-95]. Although malnutrition (i.e. weight loss, weakness and pain upon eating) may be expected to be of additional influence on quality of life, little research has been published on this topic in this type of patient.

Conclusions from the literature

The brief review of the literature, as described in the introduction of this thesis, has left us with many questions unanswered. The following issues still need attention:

1. When comparing nutrition (intervention) studies a large number of nutritional parameters have been used to identify patients at risk of malnutrition. This varies from a single parameter such as albumin (which is more reflective of stress than nutritional status) or delayed type hypersensitivity (an immune parameter rather than a measure of nutritional status per se) to complex combined nutritional risk indices;
2. Head and neck cancer is characterised by immune dysfunction while at the same time many head and neck cancer patients present with malnutrition. Whether the immune dysfunction is caused by the malignancy or underlying metabolic changes or whether the concurrent malnutrition also makes a contribution is so far not clear;
3. Nutrition intervention studies from 5 to 10 years ago have shown positive effects of peri-operative (par)enteral nutrition in severely malnourished patients[10,96]. Recent studies do, however, suggest that not all patients will benefit from peri-operative nutrition and indicate that further research is required to determine which types of patients may benefit and which may not[97,98]. However, these studies did not always include pre-operative nutrition, not all patients were malnourished and head and neck cancer patients were never involved;
4. The use of arginine as a sole immuno-modulating ingredient in a pre-operative set-

ting has never been the object of study in cancer patients;

5. It is not clear whether or not pre-operative tube feeding also attributes to the general wellbeing of the patients. On the one hand, the provision of extra energy and protein might help patients make feel stronger, whereas on the other hand, the feeding tube itself might make them feel stigmatised.

Outline of the thesis

The first part of this thesis is intended to identify the number of head and neck cancer patients who are malnourished and to describe the possible impact of this malnourished state on their treatment outcome. Chapters 2 and 3 describe the prevalence of malnutrition in a cohort of head and neck cancer patients, the best parameter for defining malnutrition in this patient population and the impact of malnutrition on postoperative outcome and long term survival. Chapter 4 examines the question of whether malnutrition contributes to immune dysfunction in head and neck cancer patients or whether this is caused by (mediators secreted by) the tumour alone.
The second part of this thesis is designed to study the possible effects of (immune-modulating) pre-operative nutritional intervention on postoperative morbidity, survival and quality of life. Chapter 5 addresses the role of pre-operative nutritional intervention with and without arginine as an immune modulating ingredient on postoperative morbidity and mortality. Chapter 6 focusses on specific immune function markers in relation to prognosis.
Finally, the effect of nutritional intervention on patients' quality of life is described (chapter 7).

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Chapter 2

Assessment of malnutrition parameters in head and neck cancer and their relation to postoperative complications

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Abstract

Background:

Malnutrition is reported frequently in head and neck cancer patients. Up to now, the impact of malnutrition on surgical outcome is not clearly understood. The purpose of this study was to define the usefulness of six different parameters in scoring malnutrition and to determine the nutritional parameter primarily related to postoperative complications.

Methods:

64 patients undergoing major surgery for advanced head and neck cancer were studied prospectively and the six different parameters were used to define malnutrition. Logistic regression was used to relate nutritional parameters to postoperative complications.

Results:

The parameters applied all identified different aspects of the nutritional status, as malnutrition varied between 20 and 67%. Logistic regression analysis identified a weight loss of more than 10% to be the most prominent predictive parameter for the occurrence of major postoperative complications.

Conclusions:

Patients with weight loss more than 10% during the six months before surgery are at great risk for the occurrence of major postoperative complications.

Introduction

Cancer patients have a relatively high incidence of cachexia. The origin of cancer cachexia is unclear. Cancer cachexia can be due to diminished oral intake and also to catabolic factors secreted by the tumor such as the cytokines tumor necrosis factor-α, interleukins, interferon-gamma or the newly detected cancer cachectic factor 24K[1]. Head and neck cancer patients are at particular risk for malnutrition for several reasons. Poor dietary habits together with excessive smoking and alcohol consumption are frequently observed among these patients. Moreover, the location of the tumor leads to dysphagia and odynophagia resulting in a reduced dietary intake[2,3,4]. Malnutrition has been reported in 30-50% of patients with head and neck malignancies, particularly the

squamous cell carcinomas of the oropharyngeal and hypopharyngeal area[2,4,5]. The apparent nutritional depletion in these patients reduces the tolerance to treatment[4,5,6].
The curative treatment of most patients with advanced (T2-T4) head and neck cancers consists of a combination of surgery and radiotherapy. Consequently, 30-50% of these patients are operated in a malnourished condition. Only a few studies on the relationship between nutritional parameters and the incidence of major postoperative complications have been performed[5,7,8]. The results of these studies suggest a relation between malnutrition and complications. However, interpretation of these studies encounters difficulties as these studies suffer from shortcomings such as small study population, indistinct definition of malnutrition or heterogeneous patient groups.
The aim of the present study was to determine, in a prospective study, the most important nutritional parameter related to postoperative complications in patients with head and neck cancer.

Patients and methods

From March 1993 to March 1994 nutritional assessment was performed on all patients admitted to the department of Otolaryngology/Head and Neck Surgery of the Free University Hospital with T2-T4 carcinomas of the oral cavity, larynx, oropharynx or hypopharynx who were eligible for surgery. All patients that entered the study had histologically proven squamous cell carcinoma. Of the 64 patients included, 44 patients had a previously untreated tumor and 20 had a recurrence after previous radiotherapy.

Nutritional assessment

Nutritional assessment was performed on the day prior to operation in stable, ambulant patients. In addition to patient and disease characteristics, the following nutritional parameters were recorded for each patient:

1. Percent weight loss during the past six months (PWL). For this purpose, actual weight was measured and usual body weight, defined as the body weight of six months ago, was asked for.
   Then PWL was calculated as:

   $$PWL = \frac{\text{usual body weight - actual body weight}}{\text{usual body weight}} \times 100$$

   More than 10% weight loss during the past six months can be interpreted as severe malnutrition[9].
2. Percent ideal body weight (PIW). To determine PIW, length and wrist circumference were used to work out frame size. Then PIW was computed as the midpoint of the weight range for a given height and frame size from the 1983 Metropolitan Life Insurance Tables[10]. PIW 80-90%, 70-79% and <69% can be interpreted as mild malnutrition, moderate malnutrition and severe malnutrition respectively[9].
3. Nutritional index (NI). A modified nutritional index[11,12] was calculated based on albumin, percentage ideal body weight and total lymphocyte count:
   $NI=(0,14 \times Alb\ (g/l)) + (0.03 \times PIW\ (\%)) + (0.73 \times TLC\ (10^9/mm^3) - 8.90.$
   An outcome less than 1.31, the mean of the reference group in the original study, was considered to be deviating from a normal nutritional status (values below zero being possible).
4. Serum albumin (Alb). Serum albumin levels were measured with the bromcresolpurple method[13]. Albumin levels between 27 and 35 g/l reflect mild depletion, between 21 and 27 g/l moderate depletion and < 21 g/l severe depletion[9].
5. Total lymphocyte count (TLC). Total lymphocyte count was calculated as:

   $$TLC = \frac{\text{\% lymphocytes x white blood cell count}}{100}$$

   With regard to nutritional status, a TLC of 1500-1800 mm^3 is considered to reflect mild depletion, 900-1500 mm^3 moderate depletion and < 900mm^3 severe depletion[9].
6. Body fat (BF) and lean body mass (LBM). Total body water, body fat and lean body mass were calculated from resistance and reactance as measured by means of Bioelectrical Impedance Analysis (BIA) (RJL Systems Inc), the theoretical hydration of fat free tissue being calculated as 0.723[14].

Nutritional support

No nutritional support was given in the pre-operative period. postoperative nutritional support was given to all patients and consisted of enteral nutrition (Nutrison®), of approximately 150% basal energy expenditure (BEE) calculated with the Harris-Benedict formula[15].

Surgical procedures

All patients underwent major head and neck surgery. 36 Patients underwent a combined resection of the tumor located in the oral cavity and/or oropharynx with en bloc uni-

Table 1.

Definition of minor and major complications

Minor complications	• Redness (>5 cm) and induration of the wound • Urinary tract infection • Respiratory tract infection: positive sputum culture or abnormal chest X-ray requiring treatment with antibiotics
Major complications	• Major wound infection: purulent drainage (spontaneous or surgical) or flap necrosis • Fistula (oro- or pharyngocutaneous salivary fistula) • Anastomotic leakage: after clinical or radiological diagnosis, necessity for operation or drainage • Respiratory insufficiency requiring ventilatory assistence for > 12 hours postoperative or mechanical renewed ventilation after detubation • Cardiac insufficiency (clinical and radiological diagnosis) requiring cardiotonics and/or diuretics or myocardial infarction confirmed on ECG or by serum enzyme elevation • Shock • Prolonged ileus > 2 days

Definition of woundinfection deduced from:

Garner JS, Jarvis WR, Grace Emori T et al. CDC definitions for nocosomial infections, Am J Infect Control 1988 (16):128-140. Johnson JT, Myers EN, Sigler BA et al. Antimicrobial propylaxis for contaminated head and neck surgery. Laryngoscope 1984(94):46-51

lateral or bilateral radical neck dissection (composite resection), 28 patients a total laryngectomy. Reconstruction was performed by primary closure (composite resection 7, laryngectomy 18 patients), myocutaneous flap reconstruction (composite resection 15, laryngectomy 9 patients) or free flap reconstruction (composite resection 14, laryngectomy 5 patients). Prophylactic antibiotic treatment (Gentamicin® and Clindamycin®) was given 3 times at the day of surgery.

Postoperative course

All patients studied were followed until discharge from hospital. Postoperative complications were recorded as none, minor, major (table 1) or non-surgical related (these included: hip fracture, furuncle, wound infection due to subcutaneous infusion and gastro-intestinal problems).

Patients that underwent total laryngectomy had a swallowing X-ray with oral contrast, to determine leakage of neopharynx, 10-12 days after their operation. In all other patients swallowing was started 8-12 days postoperatively by drinking water and gradually extended to a complete diet.

Statistical analysis

Data were summarized by means and standard deviations in each group. To compare groups, oneway analysis of variance was used. Logistic regression was used to investigate the association between patient/tumor characteristics, nutritional parameters and the occurrence of minor and major complications. A p value <0.05 was considered to indicate statistical significance; in the tables the related Fisher F values are also presented. BMDP, a computerized statistical software package was used for statistical analysis[16].

Results

Nutritional parameters

In table 2 patient characteristics and numbers of patients with deviating nutritional parameters are given. Patients with previously untreated tumors (n=44) were comparable to patients that had previously been irradiated. PIW and Alb were within normal limits for ± 80% of all patients, while NI and TLC suggested undernutrition in 67% and 56% of the patients respectively.

Complications

An uncomplicated postoperative course was observed in 24 (37%) patients. 40 Patients (63%) developed complications, either minor, major, non-surgical related or a combination of these three (table 3).

No statistical significant correlation was found between the different nutritional parameters and minor postoperative complications.

Major complications occurred in 20 patients (31%). These included not only major wound infections, but also radiologic signs of anastomotic leakage, cardiac failure, pul-

Table 2.

Prevalence of malnutrition according to different parameters among previously irradiated and untreated patients

Patient characteristics and nutritional parameters	Total group n=64	Previously untreated tumor, n=44	Earlier radiotherapy, n=20
Age (years)	61 ± 10	61 ± 11	63 ± 9
Weight (kg)	71.3 ± 14.1	72.8 ± 13.6	67.2 ± 15.0
Percentage weight loss/6 months	5.3 ± 8.9	4.9 ± 8.9	6.2 ± 9.2
Weight loss > 10% /6 months	20 (31%)	13 (30%)	7 (35%)
Percentage ideal weight (PIW)	101 ± 16	102 ± 16	99 ± 16
PIW ≥ 90%	49 (77%)	34 (77%)	15 (75%)
PIW 80 - 89%	11 (17%)	8 (18%)	3 (15%)
PIW 70 - 79%	2 (3%)	1 (2%)	1 (5%)
PIW < 80%	2 (3%)	1 (2%)	1 (5%)
Fatfree mass (kg)	54.0 ± 10.0	54.3 ± 9.4	53.3 ± 11.4
(%)	80 ± 6	76.9 ± 7.9	77.7 ± 7.7
Albumin (Alb) (g/l)	38.1 ± 4.1	38.2 ± 3.5	37.9 ± 5.2
Alb ≥ 35	51 (80%)	35 (80%)	16 (80%)
Alb 27-34	12 (19%)	9 (20%)	3 (15%)
Alb 21-26	1 (2%)	-	1 (5%)
Alb < 21	-	-	-
Nutritional Index (NI)	0.85 ± 1.04	0.94 ± 0.96	0.66 ± 1.17
NI ≥ 1.31	21 (33%)	18 (41%)	3 (15%)*
NI < 1.31	43 (67%)	26 (59%)	17 (85%)
Total lymphocyte count (TLC) (mm^3)	1850 ± 73	1910 ± 74	1710 ± 71
TLC ≥ 1800	28 (44%)	20 (45%)	8 (40%)
TLC 1500-1799	16 (25%)	12 (27%)	4 (20%)
TLC 900-1499	17 (27%)	10 (23%)	7 (35%)
TLC < 900	3 (5%)	2 (5%)	1 (5%)

* $p<0.05$ vs. previously untreated tumor

Values are expressed as mean ± SD or as numbers (%) of patients

Table 3.

Postoperative complications

Complication	Numbers of patients
None	24 (37,5%)
Minor	16 (25%)
Major	20 (31%)
• pharyngocutaneous fistula or radiologic signs of anastomotic leakage	13
• orocutaneous fistula	2
• flap failure	4
• wound necrosis	2
• respiratory insuffiency	4
• myocardiac infarction	1
• septic shock	2
Non-surgical related	12 (19%)

Numbers of patients with different complications. Several patients had more than one complication

monary insufficiency and septicaemia. Among the major complications 3 deaths were observed (two patients after surgery-related complications, one after a cardiac arrest). When logistic regression was done between the various nutritional parameters and the occurrence of major complications, recent weight loss appeared to be significantly predictive, $p<0.01$ (table 4). When indicator variables of >5%, >10% and >15% weight loss were included in the independent variable set, it was shown that more than 10% weight loss was left as the most prominent predictive parameter for postoperative complications. For patients with a weight loss of less than 10% there is only a probability of 1 in 8 that major postoperative complications occur. For the patients who have a weight loss between 10 and 15% this probability is 50/50, while for patients with a weight loss >15% this becomes 7 in 9. Setting the threshold at 10% means that the 10-15% group and the >15% weight loss group will be joined, while setting the threshold at 15% means that the 10-15% group will be joined to the <10% group. The first strategy is clearly

Table 4.

Independent variable analysis of major complications

Variable	F value	p value	F value after entering 10% weight loss	p value after entering 10% weight loss
% weight loss	10.23	0.0022	0.00	0.9795
weight loss > 5%	11.88	0.0025	0.02	0.8794
weight loss > 10%	18.99	0.0001	–	–
weight loss > 15%	9.92	0.0010	1.14	0.2900
leukocyts	7.09	0.0099	1.70	0.1968
albumin	4.84	0.0316	0.23	0.6320
sex	5.06	0.0281	1.66	0.2026
age	0.29	0.5924	1.22	0.2744
weight	3.38	0.0707	0.68	0.4129
% ideal body weight	2.21	0.1423	1.00	0.3206
lean body mass	2.51	0.1183	0.35	0.5548
% lean body mass	0.10	0.7522	0.01	0.9330
total lymfocyt count	0.01	0.9060	0.04	0.8470
nutritional index	3.64	0.0612	0.41	0.5240
type of operation	2.91	0.0929	1.00	0.3210
PM flap reconstruction	1.33	0.2528	1.76	0.1896
free flap reconstruction	0.04	0.8422	0.01	0.9075
T2	0.02	0.8911	0.64	0.4285
T3	2.14	0.1486	2.37	0.1293
T4	2.39	0.1273	0.33	0.5657
N0	0.58	0.4496	0.02	0.8903
N1	2.67	0.1072	2.67	0.1078
N2	0.13	0.7184	0.30	0.5867
previous radiotherapy	3.12	0.0824	2.81	0.0991

Results of logistic regression analysis with major complications as the outcome parameter. In the first step >10% weight loss was entered in the model

Table 5.

Changes in lean body mass and occurrence of major complications for subgroups of patients divided into three weight classes

	GROUP 1 stable weight or weight gain n=27	GROUP 2 weight loss 0-≤10% n=17	GROUP 3 weight loss >10% n=20
Lean Body Mass males (%)	78.2 ± 5.4	79.8 ± 5.4	82.6 ± 7.0
Lean Body Mass females (%)	67.1 ± 4.8	68.8 ± 8.8	72.4 ± 9.7
Major complication	7/27 (26%)	0/17 (0%)	13/20 (65%)

superior to the second considering the above-mentioned data. This explains why the >10% weight is stronger in predicting postoperative complications than weight loss >15%. Although albumin seemed to be significantly related to the occurrence of major complications when the original variable set was used, it was no longer significant after entering >10% weight loss in the model.

All other variables, such as the extent of the tumor, the type of reconstructive surgery and previous radiotherapy were of no statistical significance to the occurrence of major postoperative complications.

The lean body mass of males and females for subgroups of patients divided in three weight classes (stable weight or weight gain, weight loss 0-≤10% and weight loss >10%) was evaluated in order to detect the percentage loss of fat mass and/or lean body mass in these patients (table 5). It was clearly shown that the percentage of lean body mass did not change in patients with the different weight losses, meaning that the loss of weight was due both to loss of fat and loss of protein mass.

Major complications were also scored in the three groups. As expected most of the major complications occurred in the group of patients with a weight loss of more than 10% (table 5).

Start of swallowing

In patients with an uncomplicated postoperative course, swallowing is started 12-14 days after total laryngectomy and 8-12 days after composite resection. Prolonged time to swallowing was defined as either no swallowing or swallowing later than 14 days after total laryngectomy or later than 17 days in other patients. Stepwise logistic regression did not point out any of the nutritional parameters to show an association with prolonged time to swallowing rehabilitation. Since 'major complications' is clearly an outcome parameter, it can not be used as a predictor in the logistic regression. However, cross tabulation showed that patients with major complications, as expected, did have a prolonged time to swallowing. 9 Patients (including 3 deaths) never started to swallow again, all of them having had a major complication.

Discussion

Malnutrition is reported frequently in head and neck cancer patients. In previous studies a clear relation between malnutrition and morbidity has been shown. Most of these studies report malnutrition to be present in 35-50% of all head and neck cancer patients[4,6,7,8,17,18].

However, when looking into the definition of malnutrition in these studies, it remains often unclear how this was defined. In this study 6 accepted nutritional parameters were used to study the nutritional status of head and neck cancer patients undergoing surgery and to evaluate their relationship with postoperative complications.

It can be deduced from table 2 that malnutrition seemed to vary between 20% and 67% in the patients studied, depending on the parameter used. Therefore the reliability of each parameter in this patient group is questionable. To understand the differences in outcome the advantages and disadvantages of each applied parameter will be discussed.

The NI utilized has been derived from combinations of anthropometric, biochemical and immunological parameters to relate the risk of operative morbidity and mortality to nutritional status[11,12]. In this study, the NI classified most patients as depleted.

TLC, one of the constituents of the NI, classified 56% of the patient population as malnourished. TLC is an indicator of immune function and reflects B-cells and T-cells. It may be useful as a screening parameter with patients with a noncritical illness but increases with infection and decreases with cancer, metabolic stress and after surgery[9]. Its decrease in this population with cancer might have negatively influenced the outcome of the NI. Albumin, also one of the components of the NI, was within normal limits in 80% of the patients and consequently could not substantially influence the NI. Serum albumin is a visceral protein that reflects protein depletion in chronic rather than acute illness. During malnutrition albumin may shift from the extravascular to the intravascular space[19,20,21] which might explain its relatively normal values in this patient group. PIW, also part of the NI, demonstrated 77% of the study population to be well-nourished, which thus could not have influenced the NI. PIW can be misleading because, in this study population, a fair amount of the patients with severe weight loss showed a normal PIW, suggesting the existence of overweight before.

It may be concluded that the decrease in NI in this study population was predominantly influenced by the low TLC. However, a slight decrease in albumin in combination with a somewhat decreased PIW may also account for abnormal NI's. The NI is a set of parameters that is sensible for small changes due to metabolic stress, and must be considered as a stress or disease index more than a nutritional index.

Bioelectrical Impedance Analysis (BIA) is a relatively new method for determining total body water and (derived) body fat and lean body mass. A single frequency measurement device can only be used to determine extracellular water and total body water. In critical conditions (e.g. edema, dehydration, pregnancy, old age) the amount of extracellular water can be disturbed, herewith making the measurement and the derived calculation unreliable[14]. In this study, BIA was performed in stable patients without fluid disturbances. Percent lean body mass did not change in patients with ongoing weight loss. This means that patients with weight loss must have wasted not only fat mass but also protein stores. It seems explicable that weight loss, partly due to wasting of protein stores, decreases the resistance to postoperative metabolic stress and increases the risk of major postoperative complications.

In the present study, nutritional assessment was performed on the day prior to surgery in non-critically ill, ambulant patients. There was no question yet of any obvious acute phase response or fluid imbalance. It was, therefore, justified to assume that each parameter was measured without major distortion.

It can be concluded that in this patient group the different parameters used encountered severe difficulties in scoring malnutrition.

Nutritional assessment is important in surgical patients in general because malnutrition correlates with postoperative complications. Only a few studies up till now have defined the relation between nutritional parameters and postoperative complications in head and neck cancer patients undergoing surgery. The investigation of Robbins in 400 surgical patients indeed showed a correlation between malnutrition and wound infection, yet the definition of malnutrition was ambiguous and the surgical procedures included heterogeneous procedures including both small and extensive surgery[5]. Linn was able to prove a relationship between malnutrition and postoperative complication rate and survival in older patients, but these data are not comparable with the findings of this study because a large percentage of his patient population was treated with pre-operative nutritional support[8]. Matthews was not able to find a relationship between nutritional parameters and incidence of complications and, moreover, had to draw conclusions from an incomplete set of nutritional parameters[7].

In this study, stepwise logistic regression was performed to correlate both the different nutritional parameters and, amongst others, tumor stage, previous radiotherapy and the type of reconstructive surgery with postoperative complications. It was seen that weight loss and, to a lesser degree, albumin were predictive for postoperative complications. When the analysis was continued with weight loss dichotomized into three classes, >10% weight loss was left as the only predictor for postoperative complications, indicating that the predictive value of albumin was related to weight loss. Thus, a recent weight loss of more than 10% appeared to be of great prognostic value on the occurrence of major postoperative complications.

Conclusions

In summary we conclude that the different nutritional parameters used in the literature do not accurately reflect the nutritional status of the head and neck cancer patient, because malnutrition can vary between 20% and 67%, depending on the parameter used, as shown in this study. Relating the individual parameters and postoperative course showed that recent weight loss was the only parameter to predict major postoperative complications. Patients with more than 10% weight loss during the six months prior to surgery were at great risk for the occurrence of major postoperative complications. The findings of this study may have a major impact on surgical strategies in the future, because pre-operative nutrition might reduce postoperative complications in this patient group. In a new study we will investigate whether it is possible to counteract the adverse effects of malnutrition on surgery by pre-operative nutritional support.

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Chapter 3

The impact of nutritional status on the prognoses of patients with advanced head and neck cancer

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Abstract

Background:

Malnutrition has been recognized as a poor prognostic indicator for cancer treatment-related morbidity and mortality in general, and it is reported to affect 30-50 of all patients with head and neck cancer. In this study, the correlation of nutritional status with 3-year survival was studied prospectively in 64 patients with T2-T4 carcinomas of the head and neck who were treated surgically with curative intent; the surgery was often followed by radiotherapy.

Methods:

All patients underwent nutritional screening according to six different parameters on the day prior to surgery. Overall and disease specific survival analyses were performed with a follow-up period of at least 3 years. Survival analyses were performed with the log rank test and the Cox proportional hazards model.

Results:

Lymph node stage, nonradical resection margins, and occurrence of major postoperative complications were demonstrated to affect disease specific survival for the group as a whole. None of the investigated nutritional parameters were correlated with survival. When men and women were analyzed separately, however, a pre-operative weight loss of >5% did have a prognostic value for men. The combination of male gender, pre-operative weight loss, and major postoperative complications were related to early death.

Conclusions:

Apart from the well-known prognostic parameters lymph node stage and status of surgical margins, pre-operative weight loss and occurrence of major postoperative complications were also found to have a negative influence on the survival of male patients undergoing surgery for advanced head and neck cancer.

Introduction

Since its introduction in the 1950s, the TNM staging system has been regarded as the most important prognostic cancer classification method. However, the inability of this system to describe patient health status was considered a major disadvantage even by the originators of the TNM concept, Denoix and Schwartz[1]. It is clear that coexistent disease can strongly affect a patient's survival and options for treatment[2]. Piccirillo and Feinstein demonstrated the impact of prognostic comorbidity alone, regardless of TNM stage, on several types of cancer[3].

As early as 1932, malnutrition was recognized as a poor prognostic indicator for cancer treatment-related morbidity and mortality[4]. Weight loss[5-7], serum protein levels below 65g/L[8], low levels of albumin[9], and an impaired nutritional index[10] have all been associated with increased rates of mortality with different types of cancer. Nevertheless, these studies were hampered by retrospective design and heterogenous patient groups with respect to type of cancer, staging, and treatment. Moreover, it is clear from these reports that no consensus exists regarding the assessment of malnutrition; consequently, multiple parameters are used to define malnutrition.

Although malnutrition is reported to occur frequently in head and neck cancer patients[11-13], little attention has been paid to its prognostic effect on postoperative morbidity and survival in this specific patient category. In a previous study, we prospectively investigated the possible correlation between malnutrition and the occurrence of postoperative complications in a group of 64 patients with head and neck cancer[14]. All patients underwent major surgery with curative intent. The nutritional status was assessed using six different parameters. The only nutritional parameter that could be related to postoperative complications was weight loss of more than 10% during the 6 months prior to admission to the hospital. This patient group has now been followed for a minimum of 3 years. We report herein the correlation between nutritional status, defined by 6 different nutritional parameters, and survival for 64 patients with advanced head and neck cancer. The aim of the study was to investigate the impact of nutritional status on survival alone and in relation to other peri- and postoperative patient variables.

Patients and methods

Between March 1993 and March 1994, 64 patients admitted to the Department of Otolaryngology/Head and Neck Surgery of the University Hospital Vrije Universiteit in Amsterdam for intentional curative surgery of T2 -T4 carcinomas of the head and neck were prospectively included in the study. All patients had histologically proven squamous cell carcinoma. Fifteen patients had a recurrence after earlier radiotherapy, 5 patients had a relapse after surgery, and 44 patients had previously untreated tumors. Tumor localizations were the larynx (n=19), oropharynx (n=5), hypopharynx (n=9), oral cavity (n=30), and others (n=1). Twenty-eight patients underwent a total laryngectomy and 36 patients underwent a composite resection of the primary tumor in the oral cavity or pharynx, in conjunction with a modified radical neck dissection. Reconstruction was performed by primary closure (n=25), regional pectoral flap (n=20), or free-flap reconstruction (n=19). Pathologic TNM tumor stage (pTNM) was specified as a result of histopathologic examination of the surgical specimen.

Nineteen of the 64 patients had nonradical surgery (surgery was defined nonradical if there was macroscopic tumor involvement, microscopic tumor growth, or severe dysplasia in the margins [within 5 mm of the margins])

All patients underwent nutritional assessment on the day prior to surgery, as has been described previously[14]. This included determination of the percentage of weight loss during the 6 months before treatment, the percentage of ideal body weight, serum albumin, total lymphocyte count, nutritional index, and bioelectrical impedance analysis. The nutritional index was a complex composite formula that defined nutritional status[15].

Postoperative complications were categorized as absent, minor (including minor wound infections [redness and induration of the wound], pulmonary infections, or 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).

After a follow-up period of at least 3 years, the records of all patients were studied to assess survival and cause of death. One patient was lost to follow-up due to emigration. Survival analysis was performed for both overall survival and disease specific survival (disease-related death was defined as in-hospital postoperative death within 30 days after the last surgery, death from recurrent tumor, or death from a second primary tumor).

Statistical Analysis

The chi-square test was used to detect statistical differences between groups that could bias the study (tests for confounding).

Survival curves for all patients as well as for subgroups were made according to the Kaplan-Meier method[16]. Log rank tests were used to compare survival curves for groups of patients with different patient characteristics (univariate tests of the influence of single parameters on survival)[17].

Cox proportional hazards analysis was conducted to identify the best (combination of) variables predicting survival (dynamic tests of mutually influencing parameters on survival;

Figure 1.

Log rank statistics for the association of gender with disease specific survival

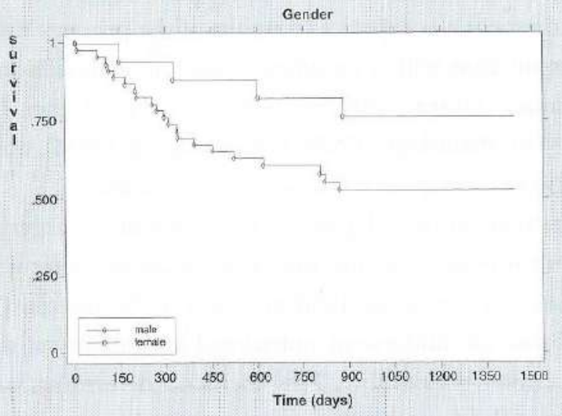


Figure 2.

The association of lymph node stage with disease specific survival (log rank p=0.0003)

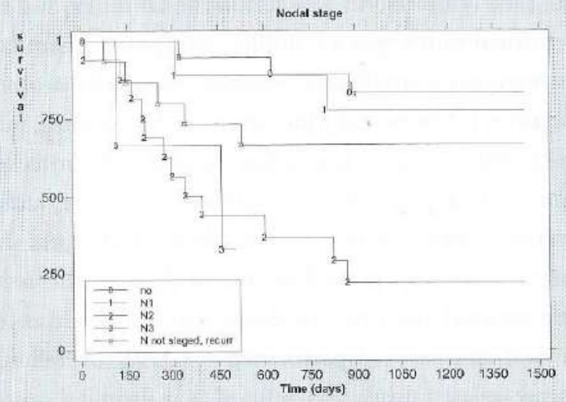


Figure 3.

The association of radical surgery with disease specific survival (log rank p=0.0009)

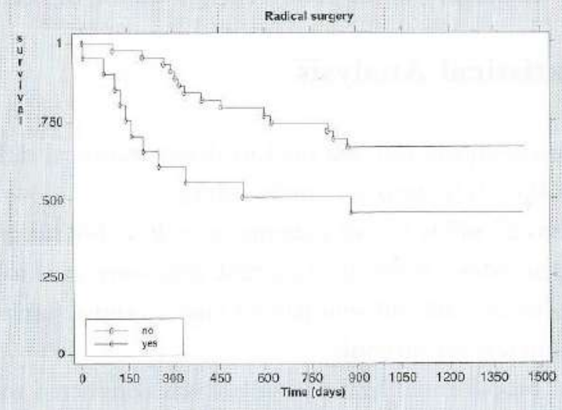
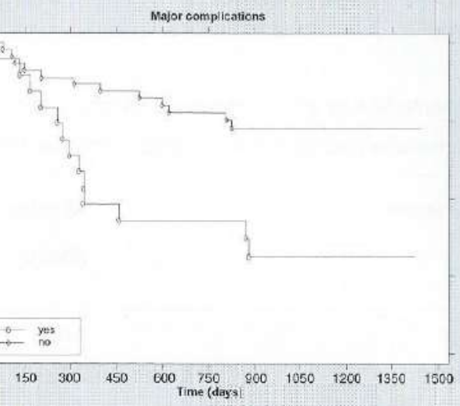


Figure 4.

The association of major postoperative complications with disease specific survival (log rank p=0.04)



variable selection was done in a stepwise and dynamic manner so that the influence of the change in parameter sets could be studied)[18].

Although patients were followed for a period of at least 3 years, the main aim of the study was to determine the duration of the period until death, if death occurred at all. The aim of the study was not to investigate whether death occurred within 3 years. This implied survival analysis techniques, rather than techniques from logistic regression and such. A P value of <0.05 was considered statistically significant.

Results

At the time of survival analysis, 29 patients had died. Overall survival was 55%, 47% for men (22 of 47) and 76% for women (13 of 17) ($P<0.05$). The main cause of death was recurrent disease (locoregional recurrence, n=6; locoregional recurrence combined with distant metastases, n=10; and distant metastases only, n=2). Three patients died of a second primary tumor. Four patients died within the first 30 days after surgery (in-hospital deaths).

Five patients were excluded from disease specific survival analysis: one patient was lost to follow-up, three patients died of causes other than cancer, and one died of an unknown cause (all of these five were men). Disease specific survival after 3 years was 61%, 55% (26 of 47) for men and 76% (13 of 17) for women (fig. 1).

To investigate the differences in survival between men and women, possible confoun-

Table 1.

Dynamic Results of Cox Proportional Hazards Analysis of Disease Specific Survival for the Total Group (Step 0), Females (Step 0), and Males (Step 0 and Final Step)

Parameter	All patients (Step 0)	Female patients (Step 0)	Male patients (Step 0)	Male patients (Final step)
Age	0.0889	0.6958	0.0845	0.0541
Gender	0.0892	-	-	-
T1,2	0.0616	0.3253	0.1157	0.6879
T3	0.3062	0.8608	0.1585	0.2249
T4	0.7799	0.2267	0.6851	0.0768
T not classified (recurrent tumor)	0.6139	0.9138	0.6779	0.6926
N0	**0.0103**	0.9499	**0.0093**	0.0673
N1	0.2273	0.4399	0.2721	0.6625
N2&3	**0**	0.3793	**0.0003**	0.7580
N not classified (recurrent tumor)	0.6139	0.9138	0.6779	0.6926
Larynx	0.3995	0.9138	0.3308	0.6583
Hypopharynx	0.6503	0.5983	0.7107	0.8857
Oropharynx	0.938	0.5983	0.9828	0.5103
Oral cavity	0.8096	0.5303	0.8096	0.9155
Weight change	0.5415	0.752	0.2078	**0.0001**
PIWeight	0.9597	0.8488	0.7929	0.3041
Albumin	0.5302	0.8753	0.2406	0.4184
Leucocytes	0.7992	0.7885	0.698	0.0866
Lymphocytes	0.261	0.2221	0.3905	0.0520
TLC	0.2363	0.7308	0.2853	**0.0204**
Radical surgery	**0.0009**	0.5431	**0.0001**	**0.0011**
Major complications	**0.0407**	0.8929	**0.0001**	0.2020
Weight loss > 10%	0.7466	0.8929	0.2024	0.1381
Weight loss > 5%	0.1307	0.6876	**0.0163**	**0.0003**
WL10 + MC	**0.025**	0.6948	**0**	0.9971
WL5 + MC	0.0624	0.9	**0**	**0.0001**
Man + MC	**0**	-	-	-
Woman + MC	0.2343	-	-	-
WL10 + man	0.0699	-	-	-
WL5 + man	**0.0018**	-	-	-
WL10 + woman	0.2343	-	-	-
WL5 + woman	0.1611	-	-	-

TLC: total lymphocyte count; PIWeight: percentage of ideal body weight; WL10: weight loss>10%; WL5: weight loss >5% plus major complication; MC: major complication.
Values represent P values; bold values represent significance and for the final step also the variables that were entered in the model.

ding variables, including known prognostic factors such as TNM tumor stage and surgical procedure, were correlated with gender using chi-square tests. None of these differences were significant.

Log rank tests were used to determine which patient characteristics influenced disease specific survival. Survival was influenced by increasing N classification (P=0.0003, fig. 2), status of surgical margins (P=0.0009, fig. 3), and occurrence of major postoperative complications (P=0.04, fig. 4). Among other factors, recurrence of tumor and age were not found to influence disease specific survival.

Because nutritional status is known to influence postoperative complications, the log rank test was also applied to patient groups as defined by the different nutritional parameters. These parameters were analyzed at fixed thresholds. No differences in survival were seen for groups of patients defined by albumin (≥35, <35 g/L), leucocytes (>9, ≤9 x 10^9/L), lymphocyte count (≥1800, <1800 x 10^9/L), percentage of ideal weight (>110%, 90-110%, <90%), weight loss (≤10%, >10%) or Nutritional Index (<0.6, 0.6-1.31, >1.31).

Interaction and predictors of mortality were studied with the Cox proportional hazards model. Our interest was to study nutritional status per se and in combination with other peri-operative and postoperative variables. We therefore also designed combinations of these factors in relation to survival. Baseline patient characteristics were included in the model to control for confounding.

Table 1, first column, shows the significant relation of these variables with survival at the start of the analysis. Of the pre-operative (combination of) variables, a high N classification (N2 or N3) and the male gender combined with pre-operative weight loss >5% were found to be predictors of decreased survival. Peri- and postoperative variables showed that nonradical surgery and especially the occurrence of major postoperative complications in men were risk factors (table 1).

Although gender is not significant at this first stage, the lower part of the results in column 1 of table 1 shows that there is a clear difference in the behavior of weight loss and major complications between the two genders. Therefore, we decided to apply the Cox proportional hazards model to each gender separately. Risk factors for a poor prognosis then appeared to be completely different between the two genders. For women, not a single variable proved to be predictive of survival (table 1, column 2). For men, however, high N classification and weight loss were shown to be separate pre-operative risk factors, whereas major postoperative complications and status of surgical margins were independent peri- and postoperative risk factors. The combination of both major postoperative complications and weight loss appeared to be even more predictive of survival (table 1, column 3). Kaplan-Meier test for combined risk factors indeed showed that men with weight loss and major postoperative complications had early deaths (fig. 5).

To assess the interrelations among variables, the variables were dynamically entered into the Cox proportional hazards model. In the final model (table 1, column 4), the following variables of interest remained: radical surgery, pre-operative weight loss (the measured value), and the grouping of weight loss, together with major complications. Total lymphocyte count also turned out to be noteworthy.

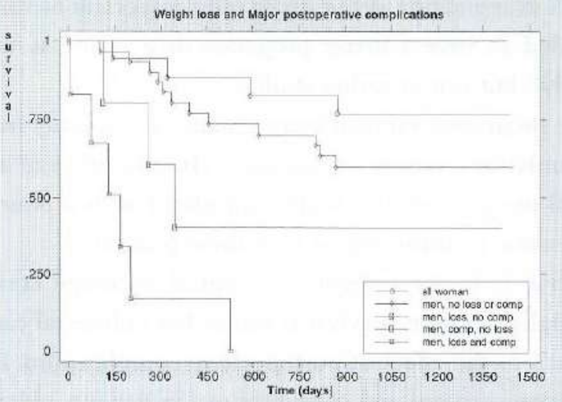
Final modeling results for all patients are not given because there is such a large gender difference in variable behavior and in the number of patients, which distorts these results considerably.

As for all patients, the relative risks for gender were computed as 2.45 (though not significant) with a confidence interval of 0.84-7.17. For men, the relative risks (and their confidence intervals) for the significant parameters were computed as 0.19 (0.07-0.51) for radical surgery, 43 (6-324) for weight loss >5%, and 77 (9-652) for the grouping of major postoperative complications with pre-operative weight loss.

Discussion

This study illustrates the prognostic value of nutritional status in addition to lymph node stage, surgical margin status, and the occurrence of major postoperative complications

Figure 5.



The association of male gender, major postoperative complications, and pre-operative weight loss with disease specific survival (log rank p=0.0000)

among male patients with head and neck cancer undergoing surgery. A surprising finding was that the outcome of survival analysis was considerably different for male and female patients. Whereas for female patients no predictive parameter could be identified (although there were only four deaths among the female patients), for male patients pre-operative weight loss was found to be a prognostic factor next to the well-known predictors of survival (had we analyzed all patients together, none of the nutritional parameters would have been identified as being prognostic value!).

An overall 3-year survival of 55% and a disease specific survival of 61% was found for patients with advanced head and neck cancer. Locoregional recurrence proved to be the major cause of death. Although 3 years seems to be a relatively short period, we know that less than 5% of tumor-related deaths will occur 3 years after treatment[19,20].

Results of survival analysis depend on the definition of the endpoint. For example, gender lost significance when only disease specific survival was studied, whereas major postoperative complications became significant. Consequently, we chose to study disease specific survival, which meant that five male patients were censored.

One might choose predictive variables from among pre-operative, peri-operative, and postoperative risk factors. Although postoperative events have no value as pre-operative prognostic variables (since they cannot be determined by pre-operative measures), they often define specific subgroups at risk. Thus, in a study assessing influences on long-term survival, their presence is clearly indicated.

For the group as a whole, N-classification, radicalness, and major postoperative complications were prognostic for survival. The impact of the N-classification is concordant with its reputation as the single most important factor in determining survival[19-23]. Females tended to have a better prognosis than males, as was also seen in a large Norwegian study[21] but not in earlier studies[19,20,22,23].

The prognostic value of margin status in surgically treated patients has been reported frequently for a variety of cancers[24,25]. In cases of head and neck cancer, tumor positive surgical margins are also highly correlated with a poor prognosis, despite the use of postoperative radiotherapy to treat these patients[26].

Literature in the category of surgical oncology concerning the effect of postoperative complications on survival is scarce. For colorectal carcinoma, conflicting data exist with regard to the effect of postoperative complications. Hessman et al. noted no correlation between survival and complications in patients older than 75 years[27]. In contrast, Bokey et al. found a poorer prognosis for patients with a postoperative complication compared with those who had no complications[28]. The same disagreement exists regarding head and neck cancer: Schantz et al. reported improved survival associated with postoperative wound infection in laryngeal carcinoma[29]. Others, on the contrary, saw increased recurrence rates and decreased survival for patients who had had a postoperative wound infection[30-33]. It is possible that the development of wound infection in the immediate postoperative period indicates a compromised immune system. Patients with a greater degree of immunosuppression may be less likely to respond adequately to bacterial contamination in the direct postoperative period and to the development of recurrent tumor in the period thereafter. Furthermore, patients with postoperative complications are likely to require more blood transfusions than patients without complications. A number of reports suggest that blood transfusion can favor tumor growth because of its immunosuppressive effect[34]. This concept was contradicted in a randomized trial in which colorectal carcinoma patients were given autologous blood transfusion[35]. These authors recently published their conclusion that the association between blood transfusion and the prognosis of a cancer patient is a result of the circumstances that necessitate transfusions, rather than an immunosuppressive effect of the transfusion itself[36]. The circumstances necessitating transfusions are most likely multifactorial, including host factors such as coagulant status and tumor factors such as complex infiltrative growth, but it is also likely that treatment-related factors, such as surgical expertise, are of importance. This may suggest that surgical expertise is an independent prognostic factor in the survival of cancer patients. It was not within the scope of this study to investigate this correlation, but there is mounting evidence that the rate of local tumor recurrence varies according to the surgeon[37].

In this study, none of the nutritional parameters were determined to have an influence on survival. This is in contrast to other studies[5-10] and might be caused by the relatively good survival of women. We therefore divided the group into females and males and analyzed the two genders separately.

In our cohort of patients, no prognostic factor could be assessed for female patients. In the group of male patients, a recent weight loss of >5%, as well as the aforementioned factors, proved to be prognostic for survival. Although in an earlier study we observed a correlation between weight loss and major complications, both parameters were independently prognostic for survival. Male patients who had weight loss as well as one or more major complications died within 1½ years after treatment.

In the literature on head and neck cancer, little attention has been paid to nutritional status and survival, although this is a patient category in which malnutrition is supposed to occur frequently. Brookes reported a significant difference between the survival of undernourished head and neck cancer patients (7.5% at 2 years) and the survival of adequately nourished patients (57.5% at 2 years) undergoing radiotherapy[11]. Nevertheless, it is very unlikely that, with adequate matching for known risk factors such as TNM stage, such considerable differences in survival could be found on the basis of nutritional status alone. Lopez et al. retrospectively studied the correlation between immunocompetence and morbidity, tumor recurrence, and survival at 2 years for 67 head and neck cancer patients undergoing surgery in conjunction with postoperative radiotherapy[38]. Those authors found a 100% survival rate for patients with a normal immunologic response and a 48% survival rate for patients with an absent cutaneous delayed hypersensitivity response. Apart from the rather unusual observation of a 100% survival rate, the results of this study must also be interpreted with caution because impaired immunocompetence is not by definition synonymous with malnutrition[39,40].

Several aspects of our study deserve comment. First of all, no data were collected regarding coexistent comorbidity, which can affect survival. Secondly, it is generally accepted that different tumor subsites within the head and neck reflect different behaviors and different prognoses. This group was too limited for such an extensive subsite analysis. Thirdly, the number of females was rather small, and this may have resulted in an inability to identify risk factors for this subgroup. Finally, we do not know whether patients who gained weight after treatment had better survival than patients who remained malnourished. This will be the focus of attention in the investigation that will extend this study.

This study reveals some of the complexity of prognostic factors for cancer patients. First of all, it highlights the impact of the TNM stage. Next, it stresses the importance of treatment-related factors, in particular the ability to obtain clear margins and avoid postoperative complications. Finally, it also demonstrates the influence of host-related factors, such as nutritional status, on survival. These findings imply that studies for determining factors related to the survival of patients with head and neck cancer should be stratified at least according to these parameters.
The adverse effect of weight loss has prompted us to initiate a prospective randomized trial to evaluate the effect of pre-operative nutritional support in resolving malnutrition in patients who are at risk.

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Chapter 4

Differences in immune status between well-nourished and malnourished head and neck cancer patients

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Abstract

Malnutrition is reported to occur in approximately 30% of head and neck cancer patients. Also, impaired immunocompetence is described as a common phenomenon in this patient group. The purpose of this study was to assess the possible relationship between malnutrition and some prognostically important immune parameters in head and neck cancer patients.

Thirty-two malnourished (recent weight loss ≥ 10%) and 34 well-nourished patients undergoing curative treatment for advanced head and neck cancer were studied prospectively, and 6 parameters of their immune status (leucocytes, lymphocytes, lymphocyte phenotyping, monocytes, HLA-DR expression on monocytes and serum interleukin-10) were determined on the day of panendoscopy. Reference values for monocytes, HLA-DR expression and interleukin-10 were obtained from 43 healthy controls. Although the number of monocytes was elevated in both patient groups, the HLA-DR expression on these monocytes was significantly lower in the malnourished than in the well-nourished and control groups. Tumor stage, tumor localisation, recurrence after initial radiotherapy, age and gender were not correlated to HLA-DR expression. No relationships emerged between nutritional status and lymphocyte subsets.

Conclusion:

Malnourished head and neck cancer patients show a significantly lower HLA-DR expression on monocytes than well-nourished ones and healthy controls. According to the literature this would imply an increased risk for postoperative complications. Indeed, postoperative complications occur more frequently in malnourished than in well-nourished patients.

Introduction

It is generally known that competent host defence mechanisms can be an important determinant in the outcome of an individual's response to neoplastic disease. Most studies on the systemic immune responsiveness in patients with head and neck (H&N) cancer have yielded evidence for a decreased immune function, especially with regard to cellular immunity. Immunosuppression appears to be more frequent and more profound in these patients than in patients with malignancies involving other sites[1]. The immune suppressive capacity of the tumor has been well established in head and neck cancer patients[2]. Whether the immune system is additionally affected by malnutrition or predisposing conditions, such as tabacco and alcohol abuse is still a question of major importance.

Patients with H&N malignancies may present with concurrent nutritional deficiencies. Most studies report malnutrition to be present in 35-50% of all H&N cancer patients, particularly in patients with squamous cell carcinoma of the oropharyngeal and hypopharyngeal area[3-6]. However, in these studies the nutritional status was poorly defined. In a recent study at our institute, a number of different nutritional parameters was used to establish the prognostic value of malnutrition in H&N cancer patients undergoing major surgery[7]. The only nutritional parameter relevant for the postoperative course appeared to be a weight loss of 10% or more in less than 6 months. This parameter was found to have a significant predictive value for the occurrence of major postoperative complications.

The purpose of the present study was to determine whether malnutrition, defined as a more than 10% weight loss during the last 6 months, is attended with prognostically important immune defects such as impaired HLA-DR expression on monocytes. Therefore, patients who were eligible for surgery for advanced head and neck cancer were prospectively screened for nutritional status and immune status.

Patients and Methods

Patients

The study population consisted of 66 patients with a histologically proven squamous cell carcinoma who were admitted to the department of Otolaryngology/Head and Neck Surgery of the Free University Hospital, Amsterdam, the Netherlands in order to receive treatment with curative intent. Nineteen patients had a recurrence after earlier radiotherapy, 47 patients had a previously untreated tumor. The primary tumor sites were larynx, oropharynx, hypopharynx and oral cavity. Thirty-two malnourished patients were included as part of a larger nutrition trial (patients were considered to be malnourished when their weight loss over the last six months exceeded 10% or more). Thirty-four consecutively admitted patients without weight loss were included as a well-nourished reference group. Patient groups were not matched for age, sex or tumor stage. Fourty-three (non-matched) healthy volunteers (15 male, 28 female, mean age 33 years, range 21-60) served as controls.

Methods

On the day of panendoscopy the following immune parameters were determined in fresh (<6 hours) heparinized venous blood after erythrocyte lysis of whole blood samples (Q-prep, the Coulter Corporation, Miami USA): the absolute numbers of leucocytes and lymphocytes, the percentages of monocytes (CD14+), pan-T-lymphocytes (CD3+), T-helper lymphocytes(CD4+), T-suppressor lymphocytes (CD8+), B-lymphocytes (CD19+), Natural Killer (NK) cells (CD16/56+, CD3-) and the percentage of NK-like T-cells (CD16/56+, CD3+). In addition, HLA-DR expression on CD14+ cells was evaluated by FACS analysis (FACStar Plus, Becton Dickinson, San Jose USA), and expressed as the ratio of the mode fluorescence intensity with and without anti-HLA-DR-FITC. All monoclonal antibodies were purchased from Becton Dickinson, San Jose USA. Plasma levels of Interleukin-10 (IL-10) were measured by ELISA (Pharmingen, San Diego USA).

Reference values for the percentage of CD14+ monocytes of leucocytes (CD14+), HLA-DR expression on monocytes and plasma levels of IL-10 were obtained from 43 healthy controls.

Statistical Analyses

Statistical analyses aimed to compare both categorical and continuous variables between the groups. The chi-square test was used for the categorical variables, mainly to detect any statistical differences between the non-matched patients groups which could bias the study.

Two sample analyses (the two taled student's-t-test) was used to compare the continuous variables. Analysis of variance was used to detect associations between patient characteristics and immunological outcome. In all statistical tests a p-value less than 0.05 was considered significant.

Results

Thirty-two malnourished and 34 well-nourished cancer patients entered the study. Patient characteristics are described in table 1. More male patients and higher TNM tumor stages were seen in the malnourished group. No differences were found between patient groups for age and frequency of recurrent tumor after intital curative radiotherapy. To check for confounding variables, we tested patients characteristics such as TNM

Table 1.

Patient characteristics

	well-nourished patients (n=34)	malnourished patients (n=32)
males/females	17/17	25/7 *
year of birth	1936 ± 12	1937 ± 10
T1/T2/T3/T4	2/18/9/5	2/7/12/11 **
N0/N1/N2,3	18/6/10	10/3/19***

* chi-square p=0.017 vs. well-nourished

** chi-square p=0.06 vs. well-nourished

*** chi-square p=0.049 vs. well-nourished

tumor stage and sex against the immunological outcome parameters. None of the found chi-squares turned out to be significant.

Expression of the HLA-DR on the monocytes was significantly lower in the malnourished than in the well-nourished and control groups, while CD14+ cells were increased in both patient groups as compared to healthy controls. The mean of the HLA-DR expression was 7.0 in the malnourished group and 10.4 in the well-nourished group ($p<0.01$, table 2). In the healthy control group, the average of the relative HLA-DR expression on monocytes was 11.7 ($p<0.001$ vs. malnourished, not significant vs. well-nourished, figure 1).

Multivariate analysis of variance was applied in order to determine which of the patient characteristics (age, sex, TNM tumor stage, tumor localisation, recurrent tumor after earlier radiotherapy, recent weight loss) were most clearly related to the degree of HLA-DR expression on blood monocytes in H&N cancer patients. It appeared that only weight loss was significantly related to HLA-DR expression on monocytes ($p=0.02$), while other factors were not.

No differences were seen between malnourished and well-nourished patients in the absolute numbers of leucocytes and lymphocytes, the percentages of pan-T-lymphocytes, T-helper and T-suppressor cells. Also, no differences were found in the number of

Table 2.

The immune status of well-nourished and malnourished H&N cancer patients

	well-nourished patients (n=34)	malnourished patients (n=32)	reference values [1]
leucocytes * 10^9/ml	7.6 ± 2.4	8.9 ± 3.1	3.0 - 10.0
lymphocytes * 10^9/ml	1.5 ± 0.7	1.5 ± 0.8	1.0 - 3.0
CD 3+ (% of lymphocytes)	71 ± 11	75 ± 10	60 - 85
CD 4+ (% of lymphocytes)	45 ± 12	46 ± 13	29 - 59
CD 8+ (% of lymphocytes)	30 ± 12	32 ± 11	19 - 48
CD 19+ (% of lymphocytes)	13 ± 7	10 ± 8	7 - 23
CD 16/56+, CD 3+ (% of lymphocytes)	3.4 ± 3.7	6.3 ± 7.8*	< 3
CD 16/56+, CD 3- (% of lymphocytes)	13.9 ± 7.5	13.5 ± 8.6	6 - 29
CD 4/CD 8 ratio	1.9 ± 1.2	1.7 ± 0.9	0.6 - 2.8
CD 14+ (% of leucocytes)	5.9 ± 2.0**	6.8 ± 3.2**	3.4 ± 1.2 [2]
HLA-DR expression on CD 14+, mode ratio	10.4 ± 6.4	7.0 ± 4.1***	11.7 ± 6.9 [2]
IL-10 (% patients with levels above detection limit)	6%	9%	0% [3]

[1] unless otherwise stated, reference values are given as the 95% distribution range in healthy adults, cording to Becton Dickinson

[2] mean ± standard deviation, based on 43 healthy controls

[3] based on 43 healthy controls

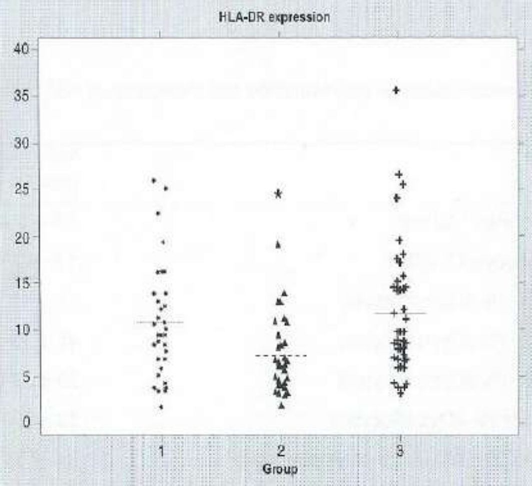
* p=0.01 vs. reference values

** p<0.001 vs. control values

*** p<0.01 vs. well-nourished patients and p<0.001 vs. healthy controls

NK-cells and the percentage of NK-like T-cells (table 2). However, malnourished patients tended to have increased numbers of NK-like T-cells compared to healthy controls. Serum levels of IL-10 were above detection limits 5 of the 66 patients and in none of the controls (table 2). The IL-10 levels were not related to nutritional status neither did they correlated with an impaired HLA-DR on monocytes.

Figure 1.
Relative HLA-DR expression (mode ratio) on monocytes in well-nourished H&N cancer patients(1), malnourished H&N cancer patients (2) and healthy controls (3)



* p < 0.01 vs. well-nourished H&N cancer patients and p<0.001 vs. healthy controls

Discussion

The primary goal of the present study was to determine differences in immune parameters between groups of H&N cancer patients with and without malnutrition, where malnutrition was defined as a weight loss of more than 10% over the last six months. It is known from the literature that the immune system in head and neck cancer patients is affected. So far, very few studies have focused on the role of malnutrition and the possible relation with immunological changes. In this study we showed that, although the number of monocytes (CD14+ cells) was increased in both patient groups, the HLA-DR expression on these monocytes was diminished in malnourished patients only. This finding was not related to TNM tumor stage, tumor localisation, sex or age of the patients.
Regarding the lymphocyte subset counts no abnormalities were found in either patient group except for NK-like T-cells, which were slightly increased only in the malnourished patients. Other investigators have found changes in lymphocyte subsets (e.g. CD4+, CD8+, CD3+ lymphocytes) related to the higher tumor stages in H&N cancer[8-10], but in our study lymphocyte subpopulations did not differ between patients with high and low tumor stages.
We were also unable to find an association between the total lymphocyte numbers and

the nutritional status, as was reported by Brookes and Clifford[11].
With regard to monocyte number and phenotype, our study confirms the findings of Garraud et al.[12] in H&N cancer patients: the numbers of peripheral blood monocytes are increased on one hand whereas the expression of HLA-DR on monocytes is impaired on the on the other hand. Garraud, however, did not pay attention to differences in nutritional status.
Recently Welsh et al. reported an impaired HLA-DR expression upon stimulation with gamma interferon in malnourished surgical patients (both cancer and non-cancer patients)[13]. This finding does support our study and suggests a correlation between monocyte impairment and malnutrition.
Class II major histocompatibility (MHC) antigens, such as HLA-DR, play a crucial role in mounting antigen specific immuneresponses to micro-organisms. But also for the induction of anti-tumor responses, the use of high quality antigen presenting cells, being strongly positive for HLA-DR and costimulatory molecules, was shown to be essential[14]. Helper T-cells respond to foreign antigens only when antigens are presented in association with "self" MHC class II molecules. Subsets of responding T-cells are thus induced to elaborate lymphokines, which in turn may attract and activate other immune effector cells, such as NK-cells, granulocytes and mononuclear phagocytes (including monocytes, macrophages, and Kupffer cells) which may then become effective killers of micro-organisms and tumor cells.
At present it is still unclear which factors cause the impaired MHC class II antigen expression in malnutrition. Recent understandings of the immunodeficiency often accompanying sepsis and multiple organ failure, make us believe that this is a result of a compensatory anti-inflammatory response. The immunosuppression seen in these circumstances often involves increased numbers of monocytes but a deactivated monocyte function (e.g. decreased HLA-DR expression, loss of antigen-presenting capacity and a reduction to produce pro-inflammatory cytokines). Patients especially at risk to develop this immune disbalance are, amongst others, patients with neoplastic disease and the elderly[15-17]. Furthermore, it is known from the literature that IL-10, prostaglandins and glutamine all may affect MHC class II expression.
IL-10 is an important immune suppressive cytokine, that has been reported to inhibit the expression of HLA-DR and to reduce the ability of cells to produce pro-inflammatory cytokines[15,16,18-21]. In a recent study with surgical patients, the postoperative fall in monocyte HLA-DR antigen expression correlated with increased levels of IL-10 messenger RNA in the mononuclear cells, but not with serum IL-10 levels[21]. Moreover,

monocytes were relatively refractory to stimulation with endotoxin, which may be a reflection of the immatureness of the monocytes. In the present study, IL-10 levels were not elevated in either the malnourished or the well-nourished patient group. The two patients with relatively high IL-10 levels (666 and 227 pg/ml) did not show extremely low HLA-DR expression (mode ratio 13.9 and 8.4 respectively). This would agree with the findings of Klava[21] where also IL-10 serum levels did not correlate with impaired HLA-DR expression on monocytes.

Also paracrine and autocrine factors have been reported to inhibit MHC-class II expression. Prostaglandins, in particular PGE2, are produced by activated macrophages and seem to decrease MHC class II expression by paracrine and autocrine effects[22,23]. Increased PGE2 production is seen in trauma patients and in patients with chronic inflammations, fever or infection. In our patient group, with advanced tumor growth, it may be that PGE2 production was increased, but plasma levels were thus far not evaluated.

Research on the influence of glutamine (GLN) on the phenotype and function of monocytes was recently done by Spittler et al.[24]. The investigators reported that lowering the GLN concentration in culture medium significantly reduced the expression of HLA-DR on monocyte-derived macrophages. Depletion of GLN was associated with a significant reduction in cellular adenosine triphosphate (ATP), wich may have influenced cell surface marker expression. A decreased GLN plasma concentration has been reported in malnourished patients[25] and may also be present in malnourished head and neck cancer patients. This will be the focus of one of our future research projects.

In this manuscript the influence of malnutrition on some parameters of the immune system in patients with H&N carcinoma was described. Malnourished patients showed a significantly lower HLA-DR expression on monocytes than well-nourished ones and healthy controls.

The central importance of HLA-DR in immune homeostasis suggests that it may be an important factor underlying the increased risk of infection in malnourished patients. Both Hershman and Polk have shown that the ability of monocytes to express HLA-DR antigen correlates directly with the clinical course in trauma patients and is predictive for the outcome with respect to both infection and death[26,27]. Döcke described that monocytic deactivation in septic patients was associated with a much higher mortality[17]. Patients with H&N cancer who have lost more than 10% weight during the last 6 months can be described as severely malnourished. This weight loss is known to have a predictive value for the occurence of major post operative complications after extensive ablative surgery[7]. In the current study, 10% weight loss was associated with a significant decrease in HLA-DR expression on blood monocytes. Since a diminished HLA-DR expression is considered to be a risk factor for both infection and death[7,26,27], it may well be that the low HLA-DR expression and the associated monocyte deactivation in malnourished H&N cancer patients plays an important role in the previously described postoperative complications. This will be an area for special attention in a future trial.

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Chapter 5

The effect of peri-operative nutrition, with and without arginine supplementation, on nutritional status, immune function markers, postoperative morbidity and survival in severely malnourished head and neck cancer patients undergoing surgery

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Abstract

Background:

Malnourished head and neck cancer patients are at increased risk of postoperative complications.

Objective:

To study the effect of peri-operative, arginine-supplemented nutritional support on nutritional status, immune status, postoperative outcome and survival in severely malnourished (weight loss > 10%) head and neck cancer patients undergoing major surgery.

Design:

49 Patients were randomized to receive either

• no pre-operative and standard postoperative tube-feeding,
• standard pre-operative and postoperative tube-feeding or
• arginine supplemented pre-operative and postoperative tube-feeding.

Results:

Patients in both prefed groups received approximately 9 days of pre-operative tube-feeding, resulting in an energy intake of 110% and 113% of calculated needs (vs. 79% in the control group ($p=0.007$)). Compared to no pre-operative feeding, pre-operative (arginine-supplemented) enteral nutrition did not improve nutritional status or any of the applied biochemical or immunological parameters. Major postoperative complications occurred in 53%, 47% and 59% of patients in each study group (NS). A trend was seen towards better survival in the arginine-supplemented group ($p=0.15$). Secondary analysis revealed that survivors showed a better HLA-DR expression on monocytes ($p=0.05$) and a higher endotoxin-induced cytokine production ($p=0.010$ for TNFα and $p=0.042$ for IL-6) at the start of the study than patients who died.

Conclusions:

9 Days of pre-operative tube-feeding, with or without arginine, does not improve nutritional status, does not reduce the surgery-induced immune suppression and does not affect clinical outcome in severely malnourished head and neck cancer patients undergoing surgery. Patients supplemented with arginine-enriched nutrition tended to live longer. There are indications that some markers of immune function may distinguish between patients with a good and a bad prognosis.

Introduction

Patients with a head and neck malignancy undergoing surgery 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 prolonged hospital stay, but also may give rise to a worse prognosis. Several factors may contribute to this morbidity, one of which is malnutrition. Most studies report malnutrition to be present in 35-50% of all head and neck cancer patients, particularly in patients with squamous cell carcinoma of the oropharyngeal and hypopharyngeal area[4-7].
In a prospective study at our institute, logistic regression was used to identify a 10% pre-operative weight loss as a predictive risk factor for the occurrence of major postoperative complications in these patients undergoing major ablative surgery[8]. Therefore the prevention or correction of nutrient depletion might be expected to minimize or eliminate malnutrition-related morbidity and mortality. In (cancer) surgery, the pooled results from 13 clinical trials suggest that pre-operative parenteral nutrition may benefit the severely malnourished patient undergoing major surgery by decreasing postoperative complications by approximately 10 percent[9]. Consensus has been reached on the duration of pre-operative feeding, i.e. 10 days (with a minimum of 7 days). This should achieve an improvement in nutritional state represented by weight gain, with no fall in blood albumin, and ideally by improved muscle strength[10]. Nevertheless, the main peri-operative parenteral nutrition trials have not analyzed the response to pre-operative nutritional treatment nor have they related changes in nutritional status due to pre-operative feeding to postoperative outcome[11-13].
Only three trials used enteral nutrition to study the impact of pre-operative nutritional supplementation on postoperative outcome[12,14,15]. In these studies, the postoperative complication rates appeared to be substantially lower in the recipients of the pre-operative enteral nutrition. However, two of those studies have been criticized because of negligent handling of data[14-16] and the best designed and executed trial[12] could not substantiate the advantage of pre-operative feeding.
Until now, the benefit of pre-operative nutrition has not been established for head and neck cancer patients. Furthermore there is no available evidence to suggest that, as far as peri-operative nutritional support is concerned, the parenteral route of administration is in any way superior to the enteral route[17]. We therefore designed a prospective, double-blind randomized trial to study the effect of pre-operative enteral nutrition on postoperative morbidity and late mortality in severely malnourished head and neck cancer patients. In one group, pre-operative and postoperative nutrition was also enriched with arginine, an amino-acid classified as semi-essential in post-traumatic states[18]. Arginine-supplementation has been associated with a positive effect on the immune status of immune depressed patients, improved wound healing, nitrogen retention, and reduced length of hospital stay[19-21]. In a recent trauma study, increased plasma arginine levels were associated with a reduction in infectious complications[22].
Studies applying arginine, omega-3-fatty acids and RNA-enriched nutrition show that this formula can modulate immune function and possibly improve clinical outcome in surgical patients[23-25]. However, arginine has never been the sole nutrient of study in a pre-operative setting.
The aim of the present study was to determine whether pre-operative enteral nutrition, with or without arginine, could improve nutritional status, reduce postoperative morbidity and surgery-induced immune suppression and improve survival in malnourished head and neck cancer patients, undergoing major surgery.

Patients and methods

Patients

From January 1st 1994 through December 31st 1997 fifty-six severely malnourished (pre-operative weight loss >10% over the past six months) head and neck cancer patients eligible for surgery who entered the department of Otolaryngology/Head and Neck Surgery of the VU Academic Hospital, Amsterdam, the Netherlands, agreed to participate in the study after having given written informed consent. Seven of these patients dropped out before being operated because they appeared not to be operable for various reasons (mostly due to 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%), received other investigational drugs or steroids, or suffered from renal insufficiency, hepatic failure, any genetic immune disorder or a confirmed diagnosis of AIDS.

Nutrition

After stratification for character of operation (combined mandibular resection or total laryngectomy) and previous radiotherapy (yes or no), the patients were randomly assigned to one of the following treatment groups on the basis of a computer generated randomi-

Table 1
Composition of the nutritional formulas

Composition per liter

	Standard formula	Arginine-supplemented formula
Protein (g)	62.50	36.85
Free arginine (g)	0.00	12.50
Glutamin (g)	6.30	3.70
Nitrogen (g)	9.80	9.80
Fat (g)	48.61	48.61
Carbohydrate (g)	140.63	153.77
Energy value (kJ)	5250	5250

Assumptions:
1 g protein = 17 kJ
1 g arginine = 17 kJ
1 g carbohydrate = 17 kJ
1 g fat = 38 kJ
glutamine content = 10% by weight of casein
conversion factor for casein = 6.38; arginine contains 32.16% nitrogen

zation schedule with an equal probability of receiving either one of the three nutritional regimens. Group 1 received no pre-operative nutritional support, group 2 received pre-operative enteral nutrition using a specially formulated product which closely reflected the current standard of practice (standard formula), and group 3 received isocaloric, isonitrogenous pre-operative enteral nutrition in which 41% of casein proteins were replaced by arginine. Nutritional solutions were isocaloric and isonitrogenous (table 1). Blinding of patients was only possible in groups 2 and 3.

Patients were given enteral nutrition at home for 7-10 days preoperatively through a naso-gastric feeding tube, unless medical circumstances necessitated admission to hospital.

Target intakes were based on estimated energy requirements, calculated as 1.5 times the basal energy expenditure (BEE) estimated by Harris and Benedict equations[26], on the basis of actual weight. Tube-fed patients (group 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 pre-operatively; no additional supplements were prescribed. Patients were requested to record all nutritional intake in a nutritional diary. In addition to recruitment, patients had at least one telephone contact with the research dietitian during the pre-operative period.

Postoperatively, all patients received tube-feeding (1.5 * BEE) , starting on the first day postoperative, until a swallowing X-ray, 10 days after operation, showed no leakage of their 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, immunological evaluation, assessment of clinical outcome and survival at the following time-points: at recruitment into the study, 1 day preoperatively, 1 day postoperatively, 4 days postoperatively, 7 days post-operatively and at the day of discharge. Follow-up time for survival was at least 16 months.

Nutritional assessment

Anthropometry and biochemistry were applied as indices of nutritional status. Anthropometric measurements included measurements of 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 (BIA, RJL Systems Inc, Clinton Twp, MI) with an age-specific computer program (Bodygram, RJL Systems Inc, Mnt S.Clemens, Detroit, MI). Skinfold thickness (biceps, triceps, subscapular and supra-iliacal) and midarm muscle circumference were used to calculate fat and lean body mass[27]. Muscle function tests consisted of measuring hand grip strength with a Jamar dynamometer (Jamar Dynamometer, Somow Engineering Co, Los Angeles, CA), reported as the most accurate for measuring grip strength under standardized conditions[28,29]. The second handle position was used as the standard to compare patients[29]. Biochemical assessment included serum albumin, electrolytes and liver and kidney function tests.

Immunologic evaluation

The following immune parameters were determined in fresh (<6h) heparinized venous blood after erythrocyte lysis of whole blood samples (Q-prep, the Coulter Corporation, Miami USA): the absolute numbers of leucocytes and lymphocytes, total lymphocyte count, the percentages of monocytes (CD14+), pan-T-lymphocytes (CD3+), T-helper lymphocytes (CD4+), T-suppressor lymphocytes (CD8+), B-lymphocytes (CD19+), natural killer (NK) cells (CD16/56+, CD3-) and the percentage of NK-like T-cells (CD16/56+/CD3+). In addition, HLA-DR expression on CD14+ cells was evaluated by FACS analysis (FACStar Plus, Becton Dickinson, San Jose USA) and expressed as the ratio of fluorescence intensity (mean ratio and peak channel) with and without anti-HLA-DR-FITC. All monoclonal antibodies were purchased from Becton Dickinson, San Jose USA.

Further, the ex vivo production of IL-6 and TNFα in whole blood-samples was measured upon stimulation with different concentrations of LPS (Difco Laboratories, Detroit MI, USA) to final concentrations of respectively 0, 0.01, 1 and 100 μg LPS/L. Samples were incubated for 4 hours (at 37° Celsius, 5% CO_2) and production of IL-6 and TNFα (ng/L) was measured in the supernatants by means of a cytokine specific ELISA (CLB, Amsterdam, the Netherlands).

Clinical outcome

Assessment of outcome was based on the peri-operative use of blood, blood-products and antibiotics, the occurrence of postoperative complications, date of swallowing and date of discharge from hospital. Postoperative complications were categorized as absent, minor (including minor wound infections - redness and induration of the wound- pulmonary infections, or 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 April 1st, 1999, after a follow-up period of at least 16 months, 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 days after the last operation, death from recurrent tumor or death from a second primary tumor.

Statistical procedures

From earlier studies it is known that 60% of malnourished head and neck cancer patients suffer major postoperative complications, whereas this is 20% in well-nourished patients[8]. To reduce the percentage of major postoperative complications from 60% in malnourished controls 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. When it appeared that patient recruitment was much slower than expected, it was, due to financial strategic reasons by the sponsor, decided to close recruitment on December 31st, 1997.

One-way analysis of variance (ANOVA) was used to compare continuous variables. Chi-square tests were employed to compare discrete variables. A 2-factor repeated measures ANOVA was applied to analyze group and time interactions. Survival curves for all patients as well as for subgroups were made according to the methods of Kaplan & Meier. Immunological tests with different baseline values at the start of the study (due to individual biological spread) were set at a 100% starting point and calculated from there. The overall pooled coefficient of variation (i.e. a time-point corrected intra-individual coefficient of variation) was computed for the data concerning cytokine production. Calculations were made with SPSS (SPSS, Chicago) and BMDP (BMDP Statistical Software, Los Angeles) computer software. All p-values of 0.05 or less were considered to indicate statistical significance. Results are presented as mean ± standard deviation, unless otherwise stated.

Results

17 Patients were allocated to group 1, 15 to group 2 and 17 to group 3. Patient characteristics are described in table 2. Groups were similar in terms of age, tumor stage, tumor localization, weight loss and comorbidity. Group 2 had relatively more women than the other two 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, free flap reconstruction) was not different between the 3 groups. For all patients, mean duration of operation was 8.6 ± 3.1 hours and mean recorded blood loss during operation 1.525 ± 1.037 L.

Table 2.

Patient and tumor characteristics

Characteristics	group 1 n=17	group 2 n=15	group 3 n=17
gender, male/female	11/6	7/8	12/5
age	55 ± 10	60 ± 8	59 ± 12
tumor stage	III: 2	III: 2	III: 3
	IVa: 11	IVa: 7	IVa: 9
	IVb: 1	IVb: 0	IVb: 0
	recurrent tumor: 3	recurrent tumor: 5	recurrent tumor: 5
		not staged: 1	
tumor localisation	oral cavity: 5	oral cavity: 2	oral cavity: 1
	larynx: 3	larynx: 3	larynx: 3
	oropharynx: 5	oropharynx: 4	oropharynx: 9
	hypopharynx: 4	hypopharynx: 5	hypopharynx: 3
		other: 1	other: 1
comorbidity yes/no	2/15	3/12	4/12
percent pre-operative weight loss	15.4 ± 5.9	17.1 ± 7.2	12.8 ± 5.1

data indicate means (± standard deviation). There were no significant differences between groups
Group 1 (n=17): no pre-operative nutritional support, standard postoperative tube feeding
Group 2 (n=15): standard pre-operative tube feeding, standard postoperative tube feeding
Group 3 (n=17): arginine-supplemented pre-operative tube feeding, arginine-supplemented postoperative tube feeding

For neither parameter were significant differences between groups noted.
In the pre-operative period, patients in groups 2 and 3 reached respectively 110% and 113% of their estimated energy requirements while patients in the non-prefed group reached only 79% ($p=0.007$). Pre-operative tubefeeding was given for 8.8 ± 1.4 (group 2) and 8.6 ± 1.4 days (group 3). Energy intake in these groups consisted merely of intake from tube feeding, only 10% (group 2) to 15% (group 3) from total intake came from oral food intake.

Nutritional assessment

Anthropometry

Table 3 shows the results of the most important anthropometric measurements before and after the period of pre-operative nutritional intervention. Baseline weight was lower in group 2 than in the other groups. This may be attributed to the larger number of females in this group. When women and men were compared separately, baseline weights for women and baseline weights for men were not different between groups. No significant changes in nutritional status were noted between the three groups as a result of nutritional intervention.

Biochemistry

Serum albumin levels differed significantly between groups at the start of the study (table 3). In the week of pre-operative intervention, mean albumin levels decreased in the group without nutritional intervention while levels did not change in the intervention groups 2 and 3 ($p=0.055$). Postoperatively, albumin levels decreased due to operation, but no differences were noted between groups.

Immunological assessment

The numbers of lymphocytes and T-lymphocytes (CD3+) as well as the percentage of T-suppressor lymphocytes (CD8+) differed significantly between groups at the start of the study. Therefore, these parameters 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 immunological parameters were significantly different between groups for leucocytes, monocytes, lymphocytes and T-helper cells, these differences were inconsistent and overall patterns were much the same.

Patients in all three groups did show profound immunological disturbances in response to the operation trauma: there was a clear drop in total lymphocyte count, especially caused by a decrease in number of T-helper lymphocytes (CD4+), a strong reduction of HLA-DR expression on monocytes (figure 1) and an increase in the number of leucocytes.

Table 3. Nutritional parameters in the pre-operative nutrition intervention period

baseline values					change after intervention				
nutritional parameters	group 1 n=17	group 2 n=15	group 3 n=17	p-value for differences between groups *1)	group 1	group 2	group 3	p-value for time by group interaction *2)	p-value for mean changes in time *2)
weight (kg)	62.8 ± 8.4	55.3 ± 8.1	61.6 ± 8.5	0.039 *3)	-0.1	0.5	0.7	0.39	0.17
fat mass (kg)	12.2 ± 8.7	10.5 ± 6.7	13.0 ± 5.8	0.61	-0.6	0.9	0.1	0.72	0.85
fatfree mass (kg)	42.1 ± 16.8	36.3 ± 17.0	47. 5 ± 6.9	0.14	-0.3	2.5	0.7	0.86	0.65
gripstrength right/left (kg)	35.3 ± 10.6/ 27.9 ± 13.9	26.7 ± 9.5/ 26.4 ± 11.0	33.6 ± 10.9 29.2 ± 14.6	0.07/ 0.84	-0.9/ +1.6	-0.1/ -1.3	+0.5/ +1.3	0.57/ 0.73	0.50/ 0.63
albumin (g/L)	37.3 ± 4.0	32.9 ± 6.4	35.9 ± 4.0	0.047	-2.3	1.7	-0.5	0.055	0.56

data indicate means ± standard deviation (left colums) or mean changes (right colums)

p values < 0.05 represent statistical significance.

1) one-way ANOVA

2) 2-factor repeated measures ANOVA

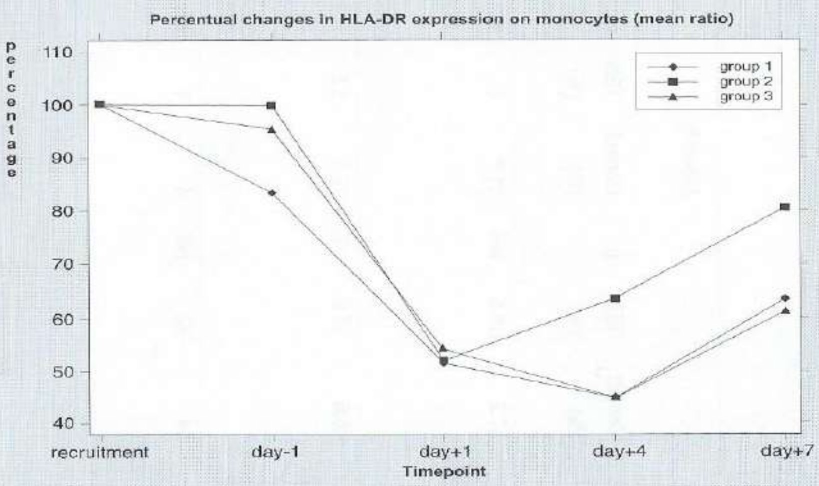
3) when calculated for men and women separately, no significant differences could be found

Table 4. Prospective randomized controlled trials evaluating pre-operative enteral nutrition

Authors	Patients	n	Nutrition Assessment Technique	Mal nou rish ed (%)	Pre-operative intervention	Result of nutritional intervention	Morbidity Endpoint	Control (%)	TEN (%)	p	Mortality Control (%)	TEN (%)	p
Shukla 1984 (14)	mixed surgery	110	anthropometric immunological and biochemical assessment	100	10 days preoperativeTEN, 3000-4000 kcal/day (n=67), no pre-operative feeding (n=43)	nutritional status improved	wound infections	37.2	10.5	NR	11.7	6	NR
Foschi 1986 (15)	bilio-pan-creatic surgery	64	weight loss >10%	50	≥12 days pre-operative TEN, 35 kcal/kg/day (n=19), TPN (n=4), TPN+TEN (n=5), no pre-operative feeeding (n=32)	no improve ment in nutritional status	any post operative complica tion	46.6	17.8	<0.01	12.5	3.5	NR
Von Meijen feldt 1992 (12)	GI cancer surgery	100	nutritional index	100	10 days pre-operative TEN, 150%*BEE (n=50), no pre-operative feeding (n=50)	NR	major compli cations	14	12	NS	4	4	NS

GI=gastro-intestinal, TEN=total enteral nutrition, TPN=total parenteral nutrition, NR=not recorded, NS=not significant

Figure 1.



Pattern of HLA-DR expression on monocytes during time
Group 1 (n=17): no pre-operative nutritional support, standard postoperative tube feeding
Group 2 (n=15): standard pre-operative tube feeding, standard postoperative tube feeding
Group 3 (n=17): arginine-supplemented pre-operative tube feeding, arginine-supplemented postoperative tube feeding

The HLA-DR expression on monocytes, which is known to be a sensitive parameter for the severity of the surgery-induced immune suppression, was comparable between groups at all time points.
The effect of surgery on the endotoxin-induced cytokine production was also very clear cut. TNFα and IL-6 production increased in the absence of or with low amounts (0.01 µg/L) of LPS. In contrast, when stimulated with 1 or 100 µg LPS/L, a sharp drop in both cytokines was seen after operation. Since patterns for TNFα and IL-6 were identical, only data of IL-6 production are given in figure 2a-2d.

Clinical outcome

Nine out of 17 patients (53%) in group 1 suffered from major postoperative complications, whilst in groups 2 and 3 these numbers were 7/15 (47%) and 10/17 (59%). The type and severity of complications (fistula formation, wound and flap complications, arterial bleeding, respiratory insufficiency) was not different between groups. Three patients died from postoperative complications, one in group 2 and two in group 3. In

Figure 2a-2d.

Pattern of IL-6 production during time upon stimulation with different concentrations of LPS

Group 1 (n=17):
no pre-operative nutritional support, standard postoperative tube feeding

Group 2 (n=15):
standard pre-operative tube feeding, standard postoperative tube feeding

Group 3 (n=17):
arginine-supplemented pre-operative tube feeding, arginine-supplemented postoperative tube feeding

CV (overall pooled coefficient of variation) for the figures 2a-2d:
panel 2a: 1.35, panel 2b: 1.37, panel 2c: 0.83, panel 2d: 0.76

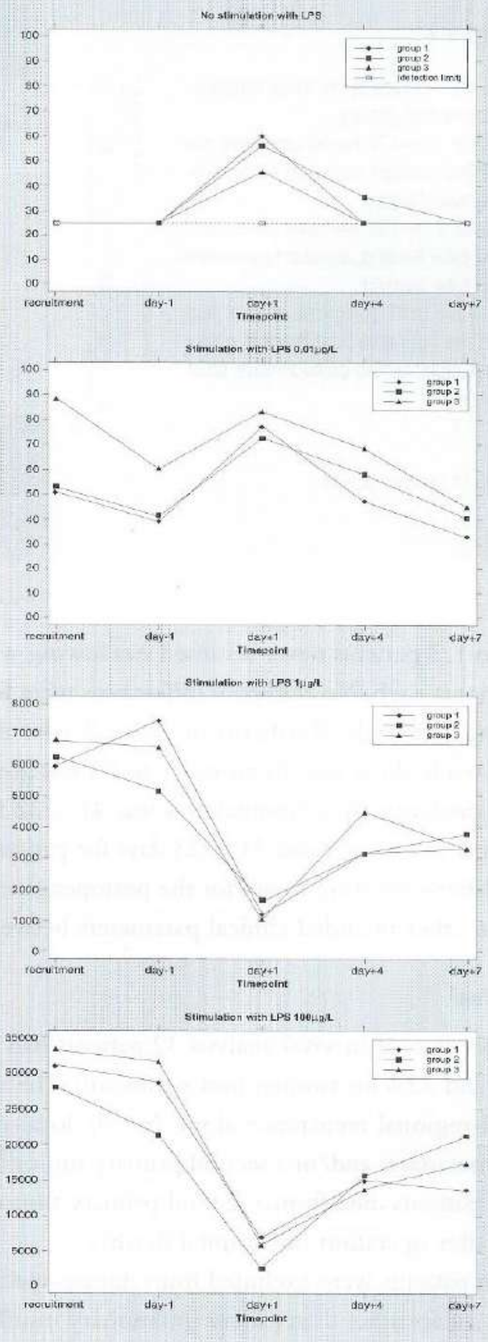
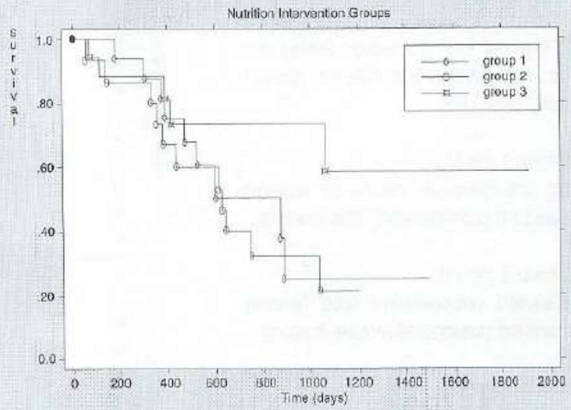


Figure 3.

Survival curves of the three nutrition intervention groups
Group 1 (n=17): no pre-operative nutritional support, standard postoperative tube feeding
Group 2 (n=15): standard pre-operative tube feeding, standard postoperative tube feeding
Group 3 (n=17): arginine-supplemented pre-operative tube feeding, arginine-supplemented postoperative tube feeding



p=0.15 between groups

group 1, 3 patients never resumed swallowing whilst for groups 2 and 3 this number was 5 patients each. No statistical differences were found for time until resumption of swallowing, although all patients in group 3 who did resume swallowing did so within 40 days, while the scatter in groups 1 and 2 was greater. The same pattern was seen for time until discharge from hospital, this was 41 ± 32 for patients in group 1, 46 ± 30 days for patients in group 2 and 31 ± 23 days for patients in group 3 (not significant).
No differences were found for the postoperative use of blood products, antibiotics or any of the other recorded clinical parameters between groups.

Survival

At the time of survival analysis 32 patients had died. Overall survival was 35%, 42% for men and 22% for women (not significant). The main cause of death was recurrent disease (local-regional recurrence alone (n= 9), local-regional recurrence combined with distant metastases and/or a second primary tumor (n=7) and distant metastases only (n=2)). Four patients died from a second primary tumor. Three patients died within the first 30 days after operation (in-hospital death).
Seven patients were excluded from disease-specific survival analysis (all men). They died from causes other than cancer (pulmonary insufficiency n=2, pulmonary embolism n=1,

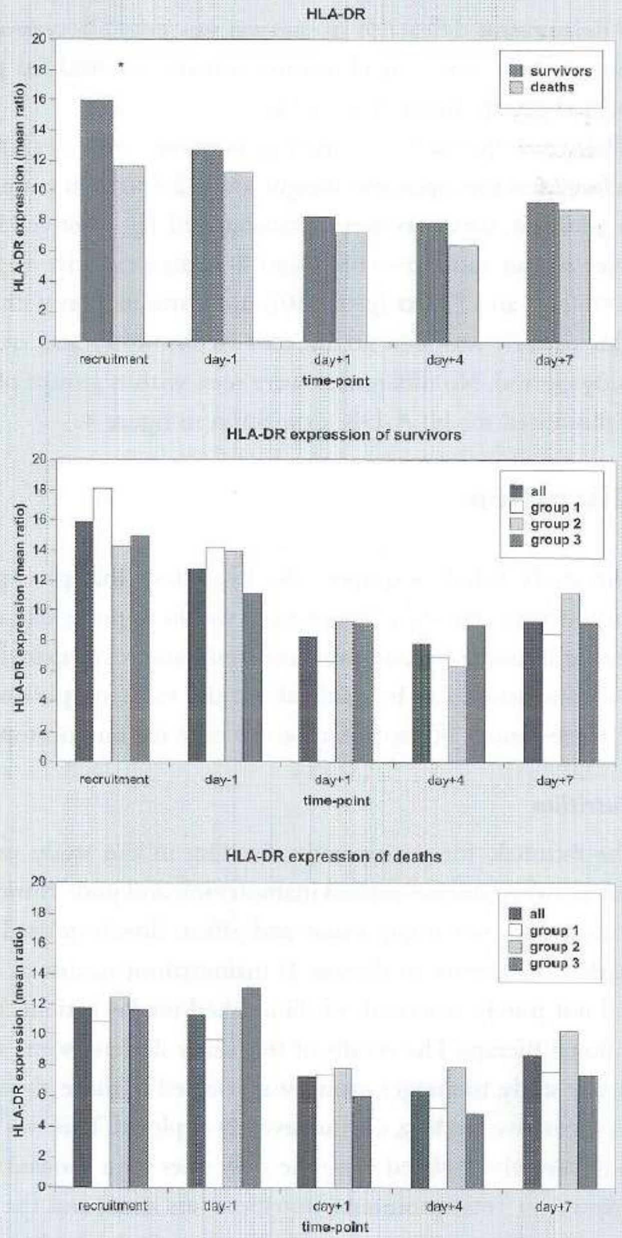
Figure 4.

HLA-DR expression of patients who later appeared to have survived (survivors) and to have died (deaths).
Data are given for all patients (figure 4a), for all survivors, divided by nutrition intervention groups (figure 4b) and for all deaths divided by nutrition intervention groups (figure 4c).

* p= 0.050 between survivors and deaths.

Survivors n=17 : group 1, n=6
group 2, n=2
group 3, n=9

Deaths n=32 : group 1, n=11
group 2, n=13
group 3, n=8



gastric hemorrhage n=1, stroke n=1, suicide n=1, 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 three nutrition groups, although there was a trend towards a better survival for patients in the arginine-supplemented group (figure 3, $p=0.15$).
When retrospectively comparing survivors with deceased, patients who survived had suffered less pre-operative weight loss (12.4%) than patients who died (16.5%)($p=0.034$) In addition, survivors were characterized by a better HLA-DR expression on monocytes (mean ratio, $p=0.050$) and a higher capacity to produce cytokines (both IL-6 ($p=0.042$) and TNFα ($p=0.010$)) upon stimulation with high doses of LPS (100 μg/L). This pattern was seen at the start of the study and continued throughout the whole study-period. No differences were seen within groups of survivors and groups of deaths as illustrated for HLA-DR expression in figure 4.

Discussion

This study failed to support the hypothesis that pre-operative feeding, either with or without arginine-supplementation, would improve clinical outcome, intermediate markers of immune function or nutritional status compared to ad libitum oral food intake. No conclusions can be made about the value op peri-operative feeding per se because all three groups of patients received tube feeding postoperatively.

Nutrition

The rationale for pre-operative feeding in this study was based on 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 severity of disease. If malnutrition occurs as a result of altered metabolism[30] and not purely as a result of diminished intake, patients are less likely to respond to nutritional therapy. The results of this study do lend some support to this hypothesis.
In this study, the target group was selected as those thought most likely to benefit from pre-operative feeding, i.e. the severely depleted. This was based on other work where the most severely depleted were the only ones who showed benefit[11]. However, in the study referred to, 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, these patients would not currently be regarded as candidates for TPN.

Three previous studies have compared pre-operative enteral nutrition with control (routine practice) (table 4). Not all patients in these studies were malnourished, head and neck cancer patients were not included and study results were not unequivocal. Moreover, the positive results of two of these studies[14,15] can be countered by criticism on the statistical handling of data[16]. The third study did not show better results for patients treated with pre-operative enteral nutrition[12].
Furthermore, the nutritional intervention may be discussed. First of all, we expected a very low food intake in the control group due to obstruction and dysphagia caused by the localization of the tumor. To our surprise, control patients consumed about 80% of their estimated requirements (vs. ±110% in both enterally fed groups). It may thus be hypothesized that although the differences in nutrient intake between the three nutrition groups were indeed statistically significant, they were too small to be clinically relevant and could explain the feeble results as described.
Secondly, 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 three groups. An explanation may be found in the fact that nutritional status was not ameliorated by nine days of pre-operative nutrition. This is in line with a study by Bruning et al.[31], suggesting that (postoperative) energy requirements for head and neck cancer patients are much higher than generally accepted. Perhaps these patients are too catabolic/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 (i.e. could incorporation of other ingredients and/or different ratios of macronutrients have possibly had an influence?).
A final consideration is that the length of nutritional support was not sufficient for repletion of these extremely malnourished patients. Seven to ten days of pre-operative nutrition has become the golden standard for patients with an approximate weight loss of 10%[9,10]. It may be hypothesized 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 are in line with the negative results of nutrition intervention studies in patients undergoing major upper GI surgery[32,33], but in contrast with the positive results in patients undergoing predominantly less invasive lower GI surgery[34,35]. This suggests that the severity of the trauma is possibly of more importance than the severity of depletion.
There is now some evidence that a positive response to nutritional therapy is a predic-

tor of clinical outcome. In COPD and HIV it has recently been shown that only responders to nutritional therapy improved their prognosis[36,37]. This raises new questions: how will we -in advance- be able to identify malnourished patients who are likely to respond to nutritional therapy? And how long a period do we need to be able to see a positive response?

Taking all this into consideration, it may thus be concluded that more work is required to determine whether earlier, more aggressive or differently composed nutritional support may be more effective in a category of extremely malnourished patients undergoing a major catabolic event. In addition, there is the challenge to find a variable that will distinguish between patients who will benefit from nutritional support and patients who will not.

Immunology

Malnutrition, head and neck cancer and surgery are all associated with impaired immune function, especially with regard to cellular immunity[38-40]. During recent years specific nutrients have been reported to improve immune responsiveness after experimental injuries[41-43]. Arginine is one such nutrient that is expected to be of benefit via its purported role on stimulating parameters of immune function, nitrogen balance and wound healing. Its supplementation (30 g/day) has been associated with increased lymphocyte blastogenic responses to mitogens and decreased number and percentage of CD8+ cells in healthy human volunteers[19]. In contrast, in surgical and in gastric cancer patients, the same amount of arginine supplementation did not induce changes in phenotypic subsets in lymphocytes, suggesting that the immune function in these categories of patients is more an intrinsic lymphocyte defect than a component of impaired nutritional status[44,45]. Studies investigating the combined effects of arginine, omega-3-fatty acids and RNA after surgery were often able to show improved immune reactions, but results regarding clinical outcome were not unequivocal[23-25,32]. Other reports contradict the immune-modulating effects of immune-enhancing enteral formulas and did not find alterations in lymphocyte and/or monocyte functions[46,47]. However, no study has tested the use of arginine as the sole variable in a pre-operative setting.

With this study, we were not able to show any noticeable immunologic differences between the arginine supplemented nutrition group and the other two groups. In all three groups, operation induced the same profound immunologic response, characterized by increased leucocytes, decreased lymphocytes and a severely depressed HLA-DR expression on monocytes. The degree of immunologic impairment induced by trauma or operation is assumed to be related to the severity of tissue injury[18]. Therefore, the extent of the trauma might have masked minor improvements in immune function in our study. The diminished ability of monocytes to express HLA-DR antigens and the delayed return to normal levels has been correlated directly with both infection and death[49-52]. This would be in line with the relatively high postoperative morbidity (>50%) in our patient groups.

The increased production of cytokines upon stimulation with no or low concentrations of LPS on day 1 postoperatively is in accordance with the literature[30]. With higher doses of LPS, this reaction was not seen (endotoxin tolerance). This state of hypo-inflammation has been described in patients with sepsis and trauma as well and is, like HLA-DR, thought to depend on the extent of trauma and to represent an autoprotective mechanism of the host to prevent 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[53-55].

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

Survival

With respect to the trend towards a better survival for arginine-supplemented patients, it can only be hypothesized how short term arginine supplementation can influence long term survival. Recent literature suggests that peri-operative restoration of the immune system by L-arginine improves immune function[44,56,57], thus reducing tumortake and thereby enhancing future survival. Possibly, a parallel may also be drawn the long-term effects of the exogenous supplementation of 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 operation are less likely to be prevented by a nutritional intervention since they are possibly related more to the severity of the illness than to any depletion in nutritional reserve[58,59].

A final remark concerns the number of patients included in the trial. Each study group consisted of 15-17 patients, which represent rather small numbers, but which is quite 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 nutrition group. For future research, we have performed a new power analysis to estimate the numbers of patients needed for a 2-armed follow-up trial comparing arginine-supplemented nutrition with control. This would need 40 patients per study-arm for a survival analysis at 3 years, with α=0.05 and a power of 80%. At 2 years, with α=0.05 and a power of 95%, these numbers would be 129 patients per study group.

Conclusion

This study failed to demonstrate a beneficial effect of 9 days of pre-operative 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 or an inappropriate choice of formula or, in part, to the modest increase in nutrient intake between the two tube-fed groups and the group fed ad lib diet preoperatively. Another explanation could be that these patients were simply too depleted to benefit from nutritional support at this late stage of their illness, and/or undergoing too great a surgical stress such that this short-term intervention was unable to have an impact. 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 pre-operative nutritional support in patients with less severe depletion is necessary to explore this hypothesis further.

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Chapter 6

Survival in malnourished head and neck cancer patients can be predicted by HLA-DR expression and IL6/TNFα response of the monocyte

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Abstract

Background:

Patients with advanced stages of head and neck cancer are often characterized by malnutrition and by an impaired immune system. Since some of the suppressed immune parameters were shown to be of prognostic importance in trauma and sepsis, we investigated whether these would also correlate with survival in head and neck cancer.

Methods:

Severely malnourished head and neck cancer patients undergoing ablative and reconstructive surgery were followed prospectively and their peri-operative immune parameters were related to long term survival.

Results:

49 Patients with a pre-operative weight loss of >10% were followed up for a period of at least 16 months after surgery. Analyses of variance revealed that pre-operative HLA-DR expression on monocytes and endotoxin-induced production of TNFα and IL-6 were different between patients who survived and patients who died. Proportional hazards identified a weight loss of more than 12%, the presence of coexistent disease and an HLA-DR expression on monocytes below the cut-off points (mean fluorescence index <15, peak channel index <9) to be of significant influence on survival.

Conclusions:

In addition to known prognostic parameters such as tumour stage, coexistent disease and weight loss, the immune parameters HLA-DR expression on monocytes and endotoxin-induced cytokine production may carry prognostic value in cancer patients. Immunomodulating therapies leading to improvement of these parameters might in the future lead to increased options for treatment.

Introduction

Patients suffering from cancer of the upper gastro-intestinal tract are at high risk of malnutrition. In head and neck cancer, approximately 35% of all patients are thought to be malnourished. This finding has recently been confirmed at our institute, whereby a 10% weight loss was found to be the best predictor of postoperative morbidity in patients

undergoing major ablative surgery[1]. Moreover, it was also found that pre-operative weight loss was predictive of a diminished survival time in men[2].
In addition to malnutrition, head and neck cancer patients are often characterized by an impaired immune status. This may be due to malnutrition, predisposing factors such as alcohol or tobacco abuse or may be a function of the malignancy itself. In an earlier study at our institute, it was found that malnutrition was indeed associated with an impaired immune response in head and neck cancer patients: malnourished patients (weight loss >10%) showed a decrease in Human Leucocyte Antigen-DR (HLA-DR) expression on blood monocytes, whereas comparable well-nourished patients did not[3]. In trauma and sepsis, HLA-DR expression on monocytes has been shown to correlate directly with the clinical course and to be predictive for outcome with respect to both infection and death[4,5]. We here report on HLA-DR expression and endotoxin-induced cytokine production in relation to prognosis in severely malnourished head and neck cancer patients undergoing surgery.

Patients and methods

From January 1st, 1994 to December 31st, 1997, 49 severely malnourished (pre-operative weight loss >10%) head and neck cancer patients eligible for curative surgery were followed prospectively and their pre-operative immune parameters were related to postoperative outcome and survival. This study took place as part of a larger nutrition trial in which patients were given peri-operative nutrition support. All patients had a histologically proven squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx and were admitted to the department of Otolaryngology/Head and Neck Surgery of the VU Academic Hospital, Amsterdam, the Netherlands. The study was approved by the Medical Ethical Committee, patients were informed of the purpose of the study, and written informed consent was obtained from all participating patients.

Immunologic evaluation

Immune parameters were obtained at the following time-points: at admission for explorative panendoscopy which was approximately 10 days preoperatively (day -10), 1 day preoperatively (day -1), and 1, 4 and 7 days postoperatively (days +1, +4 and +7 postoperatively).
The following immune parameters were determined in fresh (<6h) heparinized venous blood after erythrocyte lysis of whole blood samples (Q-prep, the Coulter Corporation, Miami USA): the absolute numbers of leucocytes and lymphocytes, total lymphocyte count, the percentages of monocytes (CD14+), pan-T-lymphocytes (CD3+), T-helper lymphocytes (CD4+), cytotoxic T-lymphocytes (CD8+), B-lymphocytes (CD19+), natural killer (NK) cells (CD16/56+, CD3-) and the percentage of NK-like T-cells (CD16/56+/CD3+). In addition, HLA-DR expression on CD14+ cells was evaluated by FACS analysis (FACStar Plus, Becton Dickinson, San Jose USA) and expressed as the ratio of fluorescence intensity (mean fluorescence index and peak channel index) with and without anti-HLA-DR-FITC. All monoclonal antibodies were purchased from Becton Dickinson, San Jose USA.
Further, the ex vivo production of IL-6 and TNFα in whole blood samples was measured upon stimulation with LPS (Difco Laboratories, Detroit MI, USA) to final concentrations of 0, 0.01, 1 and 100 ng LPS/ml. Samples were incubated for 4 hours (at 37° Celsius, 5% CO_2) and production of IL-6 and TNFα (pg/ml) was measured in the supernatants by means of a cytokine specific ELISA (CLB, Amsterdam, the Netherlands).

Survival

On April 1st, 1999, after a follow-up period of at least 16 months, the records of all patients were studied to assess survival and cause of death.

Statistical analyses

One-way analysis of variance (ANOVA) was used to compare continuous variables. Chi-square tests were employed to compare discrete variables. In order to identify prognostic parameters for survival, parameters at inclusion (day -10) were related to prognosis by means of Kaplan & Meier survival curves and Cox proportional hazards. To prevent confounding due to peri-operative interventions (i.e. nutritional support or anything else), no statistical analyses were performed between the other time-points and long-term survival. The log rank tests associated with the Kaplan & Meier curves were made to identify cut-off points for the main parameters of interest. The Cox proportional hazards model was used to identify the best (combination of) variables predicting survival (dynamic tests of mutually influencing parameters on survival; variable selection is done stepwise and dynamical so as to study the influence of change of parameter sets). Logistic regression was used to investigate the association between patient and tumour characteristics and the occurrence of major postoperative complications. Calculations were made with SPSS (SPSS, Chicago) and BMDP computer software (BMDP Statistical Software, Los Angeles). All p-values of 0.05 or less were considered to indicate statistical significance.

Table 1.

Patient and tumour characteristics

	Survivors (n=17)	Deaths (n=32)
gender (male/female)	13/4	17/15
age (mean ± sd)	59 ± 11	58 ± 10
tumour stage (n)		
stage III	4	3
stage IVa	8	19
stage IVb	1	-
recurrent tumour	3	10
tumour not staged	1	-
coexistent disease (yes/no)	2 [1] / 15	8 [2] / 24
albumin (g/L)	36.3 ± 3.6	35.1 ± 5.7
percentage pre-operative weight loss (mean ± sd)	12 ± 4	16 ± 6 *

[1] diabetes n=1, previously undetected diabetes n=1

[2] previously undetected diabetes n=3, COPD n=2, mild renal failure n=1, myelofibrosis n=1, hypertension + hyperthyreoidism n=1

* p=0.034 vs. survivors

Results

Patients characteristics are summarized in table 1. Most patients who presented with recurrent tumour were treated for recurrent laryngeal tumours after previous radiotherapy. No significant differences were noted between patients who later appeared to have survived and patients who later appeared to have died with regard to age, tumour stage, gender, albumin, coexistent disease, postoperative complications and recurrent tumour. However, patients who had died had lost more weight (16%) than patients who had survived (12%)(p=0.034).

Nutrition intervention

As part of a larger nutrition trial, patients were treated with peri-operative nutrition. The results of this nutritional intervention have been described previously[6]. In summary, patients who were given nutritional support (either none, standard or arginine-supplemented) did not benefit from this regimen. No differences were seen between the nutrition intervention groups with regard to nutritional status and clinical outcome (i.e. major postoperative complications). In the pre-operative period, nutritional status did not deteriorate nor improve (regardless of the nutritional regimen). Major postoperative complications (including wound infections requiring surgical drainage, orocutaneous or pharyngocutaneous fistula, flap failure, radiologic signs of anastomotic leakage, respiratory insufficiency, cardiac failure and septic shock) occurred in 47-59% of all patients, with no differences between the nutrition intervention groups. Logistic regression identified the tumour type (p=0.007) as the most important and the HLA-DR expression on monocytes (p=0.06) as the second most important prognostic parameter for the occurrence of major postoperative complications, regardless of the nutrional regimen.

Immunology

All patients showed profound immunological disturbances in response to surgery: there was a clear drop in total lymphocyte count, especially caused by a decrease in number of T-helper lymphocytes (CD4+), a strong reduction of HLA-DR expression on monocytes (graph 1) and an increase in the number of leucocytes.
The effect of surgery on the endotoxin-induced cytokine production was also very clear. TNFα and IL-6 production increased in the absence of or with low amounts (0.01 ng/ml) of LPS. In contrast, when stimulated with 1 or 100 mg LPS/ml, a sharp drop in both cytokines was seen after operation. Since patterns for TNFα and IL-6 are similar, only data of IL-6 production are given in graph 2.

Survival

At the time of survival analysis 32 out of 49 patients had died. For 43 patients it was more than two years after their operation, a period which is known to represent an acceptable time of follow-up since only a small percentage of tumor-related deaths will occur after that[2,7]. Survival was 35%, 42% for men and 22% for women (not significant). The main cause of death was recurrent disease (n=18). Four patients died from a second primary tumour and three patients died within the first 30 days after operation (in-hospital death). Seven patients died from causes other than cancer or from unknown causes. There was no statistical association between the occurrence of major complications (in 17/32 patients who later on died and in 6/17 patients who survived) and long-term survival (log rank, p=0.5).

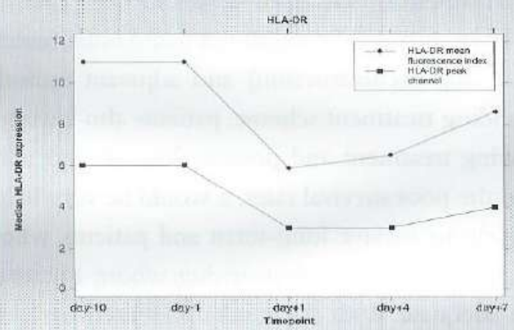
Analyses of variance revealed that survivors were, at inclusion in the study, characterized by less weight loss (p=0.034), a better HLA-DR expression on monocytes (mean fluorescence index, p=0.050, graph 3) and a higher ability to produce cytokines (p=0.010 for TNFα, p=0.042 for IL-6) upon stimulation with high doses of LPS (100 ng/ml). For the immune parameters, the patterns were most prominent (p≤0.05) at recruitment into the study, but they continued throughout the whole study period. Since patterns for IL-6 and TNFα were identical, only the graph for TNFα is given (graph 4).

Kaplan & Meier survival curves identified the following cut-off points to carry prognostic value: a weight loss of 12%, a mean fluorescence index of HLA-DR expression of 15 and a peak channel index of 9. These cut-off points as well as the absolute values were included in the Cox proportional hazards model. In this model, interactions and relations between patient and tumour characteristics, nutritional regimen, and the immune parameters were studied. The model was applied on admission variables only in order to identify early pre-operative predictors for a bad prognosis. In two steps, the model identified the presence of coexistent disease (p=0.0051) and a low HLA-DR expression (mean fluorescence index, with values below the cut-off point of 15) (p=0.03) to be the parameters with the strongest prognostic influence. The relative risk for coexistent disease could be computed as 1.38 (with confidence interval 1.13-1.68) and for a low HLA-DR expression (mean fluorescence index <15) as 2.50 (confidence interval 1.01-6.18). There was a clear relation between the mean fluorescence index (cut-off point 15) and the peak channel index (cut-off point 9) of the HLA-DR expression. So were coexistent disease and weight loss >12% also depending variables, with comorbidity carrying a higher significance (p=0.005) than weight loss (p=0.04).

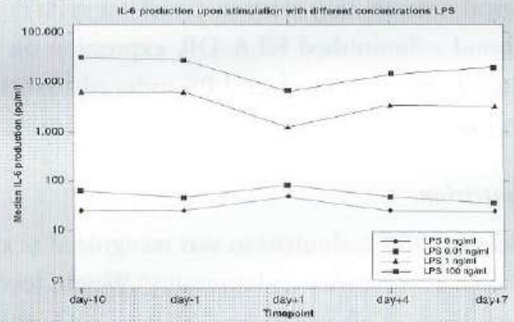
Discussion

In this study, it was shown that severely malnourished head and neck cancer patients undergoing major ablative surgery are at high risk for early death: at the time of survival analysis only 35% of the patients studied was still alive. In an earlier study at our institute it was shown that the 3-year survival rate of a comparable patient population with mainly well-nourished patients was approximately 55%[2].

Graph 1.
Pattern of HLA-DR expression on monocytes in time

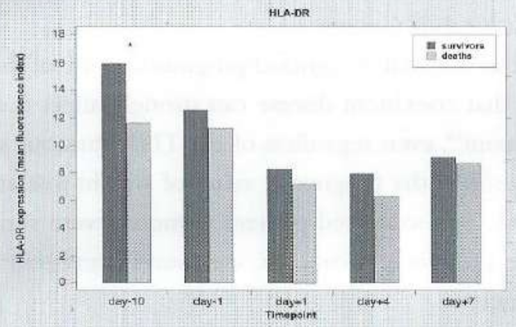


Graph 2.
Pattern of IL-6 production upon stimulation with different concentrations of LPS in time



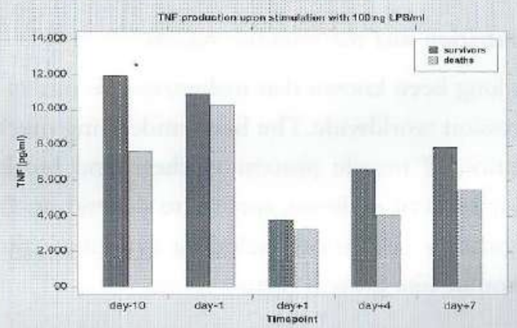
Graph 3.
HLA-DR expression (mean fluorescence index) of survivors and deaths

* p=0.050



Graph 4.
TNFα production upon stimulation with LPS 100 ng/ml of survivors and deaths

* p=0.010



The treatment of advanced head and neck cancer consists of extensive surgery (mostly total laryngectomy or combined mandibular resection in combination with pectoral flap or free flap reconstruction) and adjuvant radiotherapy. In addition to this physically demanding treatment scheme, patients also have to face a change of physical appearance following treatment and possible loss of their ability to swallow, talk or communicate. Given the poor survival rates, it would be very helpful to be able to identify patients who are likely to survive long-term and patients who are at risk for early death. With this tool, decision-making concerning whom to treat and how to treat would possibly be more adequate. With the results presented here, there are some indications that immunological markers may serve as a tool for such decision making.

We found a diminished HLA-DR expression on monocytes (proportional hazards) and a reduced ability to produce LPS-induced TNFα and IL-6 (analyses of variance) to be prognostic for a decreased survival in malnourished cancer patients prior to treatment.

Malnutrition

As early as 1932, malnutrition was recognized as a prognostic indicator for cancer treatment related morbidity and mortality[8]. Weight loss[2,9-11], serum protein levels below 65g/l[12] and low levels of albumin[13], have all been associated with increased mortality rates in different kind of cancers.

Next to the well recognized prognostic value of the higher TNM tumour stages, it is also clear that coexistent disease can strongly affect the patient's survival and the options for treatment[14], even regardless of the TNM tumour stage[15]. With the study presented here, we confirm the prognostic value of weight loss and found that even within a group of severely malnourished patients, a more severe weight loss (>12%) was predictable for a worse prognosis. Moreover, we found coexistent disease and weight loss to be related parameters.

Malnutrition and the immune system

It has long been known that malnutrition is one of the most common causes of immunosuppression worldwide. The basic underlying mechanisms, however, remain unclear. The regulation of muscle protein synthesis and breakdown, which largely determines the development of cachexia, appears to depend on the delicate balance between a number of regulatory substances including cytokines, glucocorticoids, catecholamines, insulin, and insulin-like growth factors[16].

HLA-DR

Earlier studies found the HLA-DR expression on monocytes to be impaired both in malnutrition[3,17] and in head and neck cancer[18]. Moreover, a diminished ability of monocytes to express HLA-DR has previously been shown to correlate with infection and death[4,5] in trauma patients. This study tried to find an anwer to a possible prognostic relation between immune parameters and prognosis in a homogeneous group of malnourished head and neck cancer patients.

So far, no one has ever studied HLA-DR before the traumatic event (i.e. major surgery) and correlated this with survival. This study shows that HLA-DR may serve as an additional pre-operative test of identifying patients at risk before undergoing any kind of treatment or intervention. The pattern of lower values for patients who later died was consistent throughout the whole study but of statistical significance at inclusion only. We cannot explain why the statistical significant difference disappeared at later time-points in this study. We do not think that the applied nutritional intervention may have had something to do with it, since it did not influence any of the measured nutrition or immune parameters[6]. Next to survival, we also showed that HLA-DR levels were prognostic for the occurrence of major complications. Major complications were, however, not prognostic for survival. Thus, in this study, HLA-DR has been shown to carry independent prognostic value for both short-term and long-term postoperative course.

The growing possiblities of influencing HLA-DR may offer new possibilities for the future in pretreating patients at risk, herewith improving their point of departure and possibly their prognosis. Recently, a first step towards influencing HLA-DR was made in a study at our institute. Pretreatment of patients with GM-CSF prevented the postoperative depression of HLA-DR after colorectal surgery[19]. Future studies should not only focus on the effect of immunomodulation of HLA-DR but also on its effect on clinical outcome.

Class II major histocompatibility antigens, such as HLA-DR, play a crucial role in mounting antigen specific immune responses to micro-organisms and tumour antigens[20]. Several authors have suggested that an imbalance between pro-inflammatory and anti-inflammatory responses, as seen upon severe trauma, can result in immune disturbance, which may present as a decrease in HLA-DR expression and a diminished ability to produce pro-inflammatory cytokines[21-23]. It has also been speculated that this phenomenon is a mere reflection of the immatureness of the monocytes[24]. Elderly patients and patients with cancer are known to be at increased risk for this imbalance[21]. In patients with sep-

sis, this monocytic deactivation (i.e. reduced HLA-DR expression, loss of antigen-presenting capacity and a profound reduction of the ability to produce LPS-induced TNFα) is associated with a much higher mortality[25].
This study shows, that even within a group of severely malnourished cancer patients, gradations in HLA-DR expression are found, whereby patients with lower HLA-DR expressions were more likely to die. Following this conclusion, we assessed optimal cut-off points for HLA-DR expression and used these for relative risk estimations. For the mean fluorescence index we found a a cut-off point of 15, for the peak channel fluorescence index this was 9.

Cytokines

In animal studies, the neuroendocrine systemic response to malnutrition with elevated levels of serum corticosterone was found to be a major determinant of macrophage dysfunction. This in turn may lead to decreased production of IL-6 upon stimulation with LPS[26,27], whereas a normal antigen presentation has been reported[26].
In human studies, increased cytokine levels (IL-6) and decreased cytokine production (IL-1 and IL-6) to stimulation with LPS have been reported in (cancer-)cachexia in general[28,29] and in head and neck cancer patients specifically[30-33] but these results have not been linked to prognosis. In malnourished head and neck cancer patients, improving patients' weights through megestrol acetate, an appetite stimulator, lowered the cytokine levels, thus confirming the relation between nutritional status and cytokine levels[30].
In earlier studies investigating cytokine levels in head and neck cancer, no relation was found between disease status and IL-6 production[31], but there was a relation, however, between IL-6 production and serum levels of acute-phase proteins[33], thus suggesting that IL-6 is involved in the pathogenesis of hosts' inflammatory reaction associated with tumour growth. The authors hypothesized that cytokine-levels can be used as markers of disease. In patients with oesophageal cancer, a Japanese group has indeed done so and found IL-6 levels of >7 pg/ml to correlate with increased tumour size, incidence of weight loss, tumour invasion to adjacent organs, non-curative resection and acute-phase protein response[34].
The findings of the present study confirm the hypothesis that cytokine levels may indeed be markers that distinguish between patients who are already far in the catabolic process and patients with less severe involvement. Cells of patients who later died already expressed a more severe downward catabolic trend and a greater sign of exhaustion compared to patients who survived, both preoperatively and postoperatively. What needs

to be done is to refine techniques and to define thresholds of levels predicting an advanced stage of disease.
From other studies it is known that this so called endotoxin tolerance (i.e. the inability of monocytes to produce cytokines when stimulated with the higher doses of LPS) is, like HLA-DR, thought to depend on the extent of the trauma. It has previously been observed in patients with trauma and sepsis[35-37] and is thought to represent an autoprotective mechanism of the host to prevent the detrimental effects of overwhelming cytokinaemia. However, the reaction can also be detrimental for the host, because pro-inflammatory cytokines are required to orchestrate the inflammatory response and to cope effectively with micro-organisms as well as tumour micro-metastases[35]. The results of the present study suggest that endotoxin tolerance prior to treatment is an adverse effect.

New developments

Recently, some attention has been given to mediators that coincide with catabolism and cachexia. Among these mediators, leptin has been associated with the impaired cellular immune function of malnourished patients. Leptin has been demonstrated to modulate cognate T-cell immune function and may therefore be the key link between nutritional status and an effective immune responsiveness. Indeed, leptin administration has been shown to reverse the immunosuppressive effects of starvation[38]. When translating these results to our study, it is not unthinkable that a severely nutritionally depleted patient group suffering from a major catabolic process (cancer) and demonstrating a severe immune suppression might be characterized by low leptin levels. We have not explored the hypothesis that leptin levels are decreased in the most severely malnourished patients (i.e. those who die), but it may be of interest to do so in the near future.
Another finding concerns the cancer-cachectic factor 24K, a factor that has been found in the urine of patients suffering cancer cachexia, but that is absent in the urine of patients with weight loss due to trauma or cancer patients with little or no weight loss[39]. However, in a pilot study in our hospital we were not able to identify 24K in the urine of any of our head and neck cancer patients (data not shown).

Conclusion

In this study, focusing on immune parameters and prognosis in malnourished head and neck cancer patients, we found a diminished HLA-DR expression and an impaired endotoxin-induced cytokine production to be predictive for a shorter survival in severely malnourished head and neck cancer patients before treatment. In earlier studies, these parameters were found to correlate with survival in septic patients and in trauma patients. We have related this phenomenon of immunoparalysis to survival in non-septic cancer patients before treatment. Future interventions should focus on immunomodulating therapies leading to improvement of HLA-DR expression and endotoxin-induced cytokine production.

Also, the threshold between good and bad prognostic values of HLA-DR and cytokine production must be refined. If this can be done, a step forward can be made to distinguish between how to treat, when to treat and whom to treat. This will represent an enormous improvement in medical care.

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Chapter 7

Peri-operative enteral nutrition and quality of life of severely malnourished head and neck cancer patients: a randomized clinical trial

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Abstract

Background and aims:

This study evaluated the use of peri-operative nutritional support on Quality of Life (QOL) in malnourished head and neck cancer patients undergoing surgery.

Methods:

49 Malnourished (weight loss >10%) head and neck cancer patients who were included in a nutrition intervention trial were randomized to receive either no pre-operative and standard postoperative tube-feeding (group I), standard pre-operative and postoperative tube-feeding (group II) or arginine-supplemented pre-operative and postoperative tube-feeding (group III). 31 Of these patients completed a full QOL assess-ment on the first day of pre-operative nutritional support, one day before surgery, and 6 months after surgery. Both a disease-specific (EORTC QLQ-C30) and a generic questionnaire (COOP/WONCA) were used. One way analysis of variance (ANOVA) and the Kruskal-Wallis test were applied for testing differences in scores between groups.

Results:

Between baseline and the day before surgery, both pre-operatively fed groups revealed a positive change for the dimensions physical and emotional functioning and dyspnea (with significance in group II, $p=0.050$, 0.031, 0.045 respectively). Group III showed a negative change in appetite ($p=0.049$). Between baseline and 6 months after surgery, there were no differences between group I and both pre-fed groups. There were no differences in favour of group III compared to group II.

Conclusion:

Enteral nutrition improves QOL of severely malnourished head and neck cancer patients in the period preceding surgery. No benefit of pre-operative enteral feeding on QOL could be demonstrated 6 months after surgery.

Introduction

Malnourished head and neck cancer patients undergoing radical and extensive surgery for advanced (stage III and IV) cancer are known to have a poor prognosis[1-4]. They experience a significant impact of their illness on their personal lives. Not only do they have to deal with a life-threatening illness, they also have to face a change of physical appearance following treatment and possible loss of function to swallow, talk or communicate. Therefore, optimal treatment should not only consider the clinical outcome, but also the Quality of Life (QOL) of these patients. Although QOL is a difficult concept to define, most QOL researchers agree that a QOL assessment should consider at least physical, emotional, social and functional factors. QOL studies consistently show that the disease has a significant impact on the live of these patients[5-9]. Patients experience a variety of physical problems[5,7,10], but more important is a high level of psychological distress (emotional problems like anxiety, depression, loss of self-esteem, and uncertainty about the future[5,7,11,12]). Furthermore, difficulties in social functioning such as isolation, difficult re-employment, social and sexual tensions and symptoms of fatigue and pain are commonly described[7,9,12]. It is difficult to compare these studies, because different studies used different methods to assess QOL[7,11]. Researchers agree that QOL is an important outcome measure, and as important as traditional outcomes such as survival and tumour response.

Malnutrition is reported frequently in cancer patients. Patients with head and neck malignancies are at particular risk of developing nutritional deficiencies: besides cancer cachexia the localisation of the tumour may cause poor nutrient intake, resulting from dysphagia and odynophagia (dysphagia resulting from pain) or organic obstruction. Most studies report malnutrition to be present in 35-50% of all head and neck cancer patients[1-3,6,13-17]. This has recently been confirmed at our own institute[4]. Malnutrition is clearly associated with poor response to cancer therapy, immune suppression, poor wound healing, and decreased survival[1-3]. Earlier studies suggest that severely malnourished patients might benefit from peri-operative nutritional supplementation leading to a reduction of morbidity and mortality due to postoperative complications[18-20]. Because nutrition is an important factor in the well-being of a patient, this intervention might as well have a positive impact on the QOL of these patients, but this has not yet been reported.

The objective of the present study was to evaluate the use of peri-operative enteral nutrition on the QOL of severely malnourished head and neck cancer patients undergoing extensive ablative surgery.

Patients and methods

Patients and nutritional intervention

From 1994 through 1997 forty-nine severely malnourished (pre-operative weight loss >10%) head and neck cancer patients eligible for surgery that entered the Department of Otolaryngology/Head and Neck Surgery of the VU Academic Hospital, Amsterdam, the Netherlands, participated in a peri-operative nutrition intervention study. The study was approved by the Medical Ethical Committee of the VU Academic Hospital. Before study-entry, patients were informed of the purpose of the study, and written informed consent was obtained from all participating patients. QOL was investigated as part of this larger study.

All patients had a histologically proven squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx and required major ablative surgery. Patients were excluded from the study if they were well-nourished (weight loss <10%), received other investigational drugs or steroids, or suffered from renal insufficiency, hepatic failure, any genetic immune disorder or a confirmed diagnosis of AIDS.

After stratification for the type of operation (combined mandibular resection or total laryngectomy) and previous radiotherapy (yes or no), the patients were randomly assigned to one of the following treatment groups: group I received no pre-operative nutritional support, group II received a 'standard' pre-operative enteral nutrition (1250 kcal/L, 62.5 g. protein/L) and group III received iso-caloric, iso-nitrogenous pre-operative enteral nutrition whereby 41% of casein proteins were replaced by arginine.

Blinding of patients, health care professionals involved in patient treatment and assessors was only possible in groups II and III. Patients were fed preoperatively for 7-10 days. Postoperatively, all patients were tubefed for approximately 14 days, as is the standard hospital procedure. Groups I and II were given the standard solution, whereas group III received the arginine-supplemented enteral nutrition. Caloric needs were estimated using the Harris and Benedict equation[21]. Patients were to receive 150% of Basal Energy Expenditure (BEE).

Patients were asked to complete a baseline Quality of Life assessment at recruitment into the study, the day preceding surgery, the day of discharge, and 6 months after surgery. The patients had access to the dietitian for assistance if needed.

Questionnaires

To measure Quality of Life two questionnaires were used: the cancer-specific EORTC

QLQ-C30 and the generic COOP/WONCA charts.

The cancer-specific EORTC QLQ-C30 (version 1.0) is concerned with various disease and treatment consequences that are relevant to a wide range of cancer patients. It has been developed bij the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Study Group, field-tested and refined in a broad spectrum of international trials. The QLQ-C30 exhibits adequate to excellent levels of reliability and validity, is considered suitable for repeated testing and has been validated for the use in head and neck cancer patients[5,22-24]. It was used with permission of the EORTC Quality of Life Study Group.

The QLQ-C30 incorporates five functioning scales: physical functioning (PF), role functioning (RF), emotional functioning (EF), social functioning (SF), cognitive functioning (CF), a global health status (Overall Quality of Life), and three symptom scales: fatigue, nausea and vomiting, and pain. Furthermore, it includes five single items assessing additional symptoms that are commonly reported by cancer patients (dyspnea, sleep disturbance, appetite loss, constipation and diarrhea) and a question about perceived financial impact. A one-week time-frame is used.

All scales and single items are scored on a four-point Likert scale (with responses ranging from 'not at all' to 'very much'), except PF and RF (dichotomous-response categories) and the global health/QOL scale (seven-point scale). The raw scores are transformed to a linear scale from 0 to 100[24]. A high score for a functioning scale represents a high level of functioning and better global QOL, whereas a high score for a symptom scale or item indicates a high level of symptoms/problems.

COOP/WONCA charts are generic charts (i.e. not specific for cancer patients), developed and refined by the Dartmouth Primary Care Cooperative Information Project to obtain a brief, practical and valid method to assess the functional status of adults and adolescents. The charts have been tested in many different studies to evaluate and establish their reliability, validity and acceptability[25-28]. There are six charts, covering the areas of physical fitness, mental health, daily activities, social activities, change in health and overall health. Each chart consists of a title, a question referring to the status of the patient over the past 2 weeks, and five response choices. The levels on the scales are illustrated with pictograms. All scales are scored on a five-point ordinal scale. In all scales lower scores indicate better functioning, except for the 'change in health' scale, where the middle score represents no change, and lower/higher score indicates better/worse health.

Statistics

For descriptive purposes, we used median and InterQuartile Range (IQR) for the ordinal data of the COOP/WONCA charts, and mean and Standard Deviation (SD) for the transformed data of the QLQ-C30.

In both questionnaires, we compared the scores between groups at each measurement moment as well as the changes in scores between measurement moments. For comparison between groups in the COOP/WONCA charts, we applied the non-parametric Kruskal-Wallis test using the original (ordinal) scores on the five-point scale, as recommended[25]. The raw scores of the QLQ-C30 questionnaire were transformed to a linear scale from 0 to 100 according to the EORTC scoring manual[24], and one-way analysis of variance (ANOVA) was used for testing differences between groups at each moment of follow-up. Changes in scores between measurement moments were calculated by subtracting the baseline score for each dimension and patient from the score on the day preceding surgery, the day of discharge and 6 months after surgery, respectively. Statistical significance of the change scores was tested by means of the Kruskal-Wallis test (COOP/WONCA charts) and ANOVA (QLQ-C30). For data management and -analysis, SPSS version 7.5 was used. A p-value <0.05 was considered to represent significance.

Results

Patients

Forty-nine patients participated in the nutrition intervention trial. One patient was excluded from the QOL assessment because of lack of knowledge of the Dutch language. In 1994, 17 patients received the COOP/WONCA charts only. In February 1995 also the QLQ-C30 questionnaire became available and 31 patients filled in both questionnaires. Since the patients who completed both the COOP/WONCA charts and the QLQ-C30 differed from the group of patients that exclusively completed the COOP/WONCA charts with regard to sex and comorbidity, we decided to analyse only the results of the 31 patients who completed both questionnaires. Baseline characteristics of these patients are shown in table 1. No significant differences were noticed between groups, except for a slight imbalance in tumour site ($p=0.051$) between group III and groups I and II. This is not reflected in the type of surgical treatment, or other patient or treatment characteristics, so this is not accounted for in the analysis. Due to a large number of missing values at the third measurement point (the day of discharge),

Table 1.

Patient characteristics at baseline

	Group I (N=11)	Group II (N=10)	Group III (n=10)	P-value
Mean age (range)	56.6 (42-76)	58.6 (43-69)	61.4 (43-83)	0.586
Sex	7 male	3 male	6 male	0.835
	4 female	7 female	4 female	
Tumour site	4 oral cavity	1 oral cavity	0 oral cavity	0.051
	2 oropharynx	3 oropharynx	6 oropharynx	
	2 hypopharynx	3 hypopharynx	1 hypopharynx	
	3 larynx	2 larynx	2 larynx	
		1 others	1 others	
Stage of disease	2 III	2 III	3 III	0.514
	6 IVa	4 IVa	5 IVa	
	1 IVb	3 recurrence	2 recurrence	
	2 recurrence	1 unstaged		
Surgical treatment	5 laryngectomy	5 laryngectomy	4 laryngectomy	0.813
	6 commando[1]	5 commando	6 commando	
Reconstruction	4 primary closure	2 primary closure	2 primary closure	0.147
	2 PM flap[2]	1 PM flap	1 PM flap	
	4 free flap	4 free flap	3 free flap	
	1 others	3 others	4 others	
Previous radiotherapy	9 none	7 none	8 none	0.908
	2 yes	3 yes	2 yes	
Comorbidity	9 none	8 none	7 none	0.267
	2 diabetes mellitus	1 diabetes mellitus	1 COPD[3]	
		1 hyperthyroidism	1 emphysema	
			1 kidney failure	

[1]combined mandibular resection
[2]pectoralis major flap reconstruction
[3]chronic obstructive pulmonary disease

and due to a wide variety in day of discharge between patients, we decided not to analyse these data. Eight patients were missed for QOL assessment 6 months after surgery: three patients died (groups II,III,III), one patient was too sick (group II), two patients refused to fill in the questionnaires (groups I,III) and two patients didn't show up (groups I,II). Comparison of the group of patients who completed the questionnaires at 6 months postsurgery with the group of patients who discontinued, revealed no significant differences in gender, tumour site, stage of disease, surgical treatment and reconstruction, and comorbidity. However, patients who discontinued were older (67.1 vs 55.8 years, p=0.005) and 50% had been operated for a recurrent tumour after previous radiotherapy, compared with 15% in the group of patients who continued the study (p=0.031).

QOL Questionnaires

Baseline comparison

The baseline results of the QLQ-C30 are shown in table 2. There were no significant differences between groups in the functioning scales. In the symptom scales however, there were significant differences in two scales: the dimension dyspnea differed significantly between groups I and II (p=0.021), whereas the dimension sleep disturbance differed between groups I and III (p=0.016), both in favour of group I. Comparison of baseline scores of the COOP/WONCA charts revealed no significant differences between groups (table 3). Group II showed a tendency toward lower mean scores, while group I showed a tendency toward higher mean scores for the majority of items. This was accounted for in interpreting the results.

Comparison of change scores between baseline and the day preceding surgery

Comparison of change scores of the QLQ-C30 revealed that physical functioning (PF) improved significantly in groups II and III, while worsening in group I. The change in PF was significant between groups I and II (p=0.050, table 4). Although the trends in change in scores of the COOP/WONCA charts reflected a similar change, the differences were not significant. Likewise, comparison of change scores of the QLQ-C30 showed that emotional functioning (EF) improved in groups II and III, while stabilizing in group I. The change in EF was significant between groups I and II (p=0.031, table 4). The trends in change in scores of the COOP/WONCA charts indicated a slight improvement in mental health in all groups, but these differences were not significant. The same pattern was seen for the QLQ-C30 symptom scale dyspnea (deterioration in group

Table 2.

Baseline values EORTC-C30

Baseline values EORTC-C30	Group I (n=11) mean	SD	Group II (n=10) mean	SD	Group III (n=9) mean	SD
functioning scales						
Physical Functioning (PF)	70	20	50	29	71	30
Role Functioning (RF)	77	26	65	47	67	35
Emotional Functioning (EF)	61	23	46	22	55	33
Cognitive Functioning (CF)	79	18	65	29	80	23
Social Functioning (SF)	82	19	63	32	78	25
Global health (GH)	54	18	34	22	39	21
symptom scales						
Pain (PA)	56	31	45	38	61	32
Nausea and Vomiting (NV)	9	21	30	36	2	5
Fatigue (FA)	52	23	67	25	53	32
single items						
Dyspnea (DY)	15*	23	50*	28	37	31
Sleep disturbance (SL)	21**	27	53	39	70**	42
Appetite loss (AP)	54	40	52	38	30	35
Constipation (CO)	9	21	27	38	26	32
Diarrhea (DI)	3	10	10	16	7	15
Financial Impact (FI)	9	21	23	39	30	39

A high score for a function scale represents a high level of functioning and better global QOL, whereas a high score for a symptom scale or item indicates a high level of symptoms/problems. * p=0.021 ** p=0.016.

I, improvement in groups II and III, with a significant difference between groups I and II (p=0.021, table 4). In contrast, the symptom scale appetite loss improved in groups I and II, and worsened in group III, with a significant difference between groups I and III (p=0.049, table 4). Since results of COOP/WONCA charts did not reveal significant changes, data are not given in the tables.

Table 3.

Baseline values COOP/WONCA

baseline values COOP/WONCA charts	Group I (n=11) median	IQR	Group II (n=10) median	IQR	Group III (n=9) median	IQR
physical fitness	3	3-4	4	3.5-4	4	3-5
mental health	3	2-4	3.5	2-4	3	2-4
daily activities	3	1-4	3	3-4	3	2-4.5
social activities	3	2-4	3	1.75-4.252	1-3.5	
change in health	3	3-3	3	2-3.25	2	2-4
overall health	4	3-4	4	4-4.25	4	4-5

In all scales lower scores indicate better functioning, except for the 'change in health' scale, where the middle score represents no change, and lower/higher score indicates better/worse health. IQR=difference between 75th and 25th percentile.

Significant differences between groups were neither found after testing the change scores of the remaining functional scales and symptom scales of the QLQ-C30, nor in any of the dimensions of the COOP/WONCA charts.

Comparison of change scores between baseline and 6 months after surgery

Testing change scores of the QLQ-C30 showed significant differences between groups II and III in the functioning scale cognitive functioning (p=0.033) and in the symptom scale appetite loss (p=0.040), both in favour of group II (table 5). No significant differences between groups were found after testing the COOP/WONCA charts.

Comparison QOL assessments between groups at the day preceding surgery and 6 months postoperatively

Testing the QLQ-C30 and the COOP/WONCA charts revealed no significant differences between groups on the day preceding surgery and 6 months after surgery.

Table 4.

Physical Functioning, Emotional Functioning, Dyspnea and Appetite Loss EORTC QLQ-C30

	Group I		Group II		Group III	
	mean	SD	mean	SD	mean	SD
Physical Functioning EORTC QLQ-C30, baseline value	70	20	50	29	71	30
Physical Functioning EORTC QLQ-C30, the day preceding surgery	58	19	62	23	79	22
Emotional Functioning EORTC QLQ-C30, baseline	61	23	46	22	55	33
Emotional Functioning EORTC QLQ-C30, The day preceding surgery	59	27	66	15	70	20
Dyspnea EORTC QLQ-C30, baseline	15	23	50	28	37	31
Dyspnea EORTC QLQ-C30, the day preceding surgery	21	27	30	31	26	28
Appetite Loss EORTC QLQ-C30, baseline	54	40	52	38	30	35
Appetite Loss EORTC QLQ-C30, the day preceding surgery	36	35	33	31	42	29

A high score for a function scale represents a high level of functioning. The change in PF is significant between groups I and II (p=0.050). The change in EF is significant between groups I and II (p=0.031). A high score for a symptom scale or item indicates a high level of symptoms/problems. The change in dyspnea is significant between groups I and II (p=0.021), whereas the change in appetite loss is significant between groups I and III (p=0.049)

Table 5.

Cognitive functioning and Appetite loss EORTC QLQ-C30

	Group I		Group II		Group III	
	mean	SD	mean	SD	mean	SD
Cognitive functioning EORTC QLQ-C30, baseline	79	18	65	29	80	23
Cognitive functioning EORTC QLQ-C30, 6 months following surgery	87	14	83	32	76	25
Appetite loss EORTC QLQ-C30, baseline	54	40	52	38	30	35
Appetite loss EORTC QLQ-C30, 6 months following surgery	26	32	14	26	55	40

A high score for a function scale represents a high level of functioning and better global QOL, whereas a high score for a symptom scale or item indicates a high level of symptoms/problems. The changes in CF and appetite loss are significant between groups II and III (p=0.033 and 0.040, respectively)

Discussion

This study demonstrated a positive effect of pre-operative enteral nutrition on QOL in severely malnourished head and neck cancer patients in the period preceding surgery. Patients receiving pre-operative enteral nutrition experienced a positive effect with respect to physical functioning and emotional functioning. No differences in favour of the arginine supplemented nutrition compared to the standard nutrition could be demonstrated. The COOP/WONCA charts revealed no significant differences, suggesting that this instrument is not sensitive enough to detect differences between groups in this population.

Pre-operative effects

Analysing the QLQ-C30 revealed significant improvements for the functioning scales physical functioning and emotional functioning, and for the symptom scale dyspnea in both pre-fed groups (table 4). Baseline scores tended to be lower in groups II and III, resulting in a relatively large potential to improve. Actual improvements in groups II and III coincided with a worsening of scores in group I, resulting in a clinically significant change.

The dimensions physical functioning and emotional functioning were also assessed by the COOP/WONCA charts. Although the COOP/WONCA charts show changes in the same direction as the corresponding items of the QLQ-C30, there were no significant differences. In the COOP/WONCA charts, each dimension is operationalized by only one question, while the functioning scales in the QLQ-C30 are based on multiple questions, specifically aimed at cancer patients. Therefore, the QLQ-C30 is specifically sensitive to changes in health status of cancer patients, which explains the different results of the two questionnaires. We can conclude that, although the COOP/WONCA charts showed changes in the same direction as the QLQ-C30, this instrument is not sensitive enough to detect the subtle differences that the QLQ-C30 revealed.

The finding that the symptom scale appetite loss reveals a higher level of symptoms in group III could be explained by the fact that being tubefed with 150% of Basal Energy Expenditure has a negative effect on one's appetite. Nutritional intake in group III was 113% of calculated intake, whereas it was 110% in group II, and 79% in group I. Not only did group III receive the highest nutritional intake of both pre-fed groups, previous studies also have described mild gastrointestinal side-effects of arginine supplementation, such as anorexia, bloating and diarrhoea[29-32], which might explain the higher level of appetite loss.

In summary, we conclude that pre-operative enteral nutrition results in improved physical and emotional functioning of malnourished head and neck cancer patients in the period preceding surgery. This improvement is achieved at the expense of appetite, while potentially achieving a positive change in other symptoms, in particular dyspnea, at the same time. Furthermore, the possible negative impact of carrying a tube in one's nose for ten days, which undoubtedly has an impact on one's personal life and activities, was not reflected in the QOL scores of groups II and III.

Postoperative effects

It would have been interesting to analyse the data at the day of discharge. Due to logistic problems, too many data were missing. Furthermore, the day of discharge varied widely among patients. Other longitudinal studies have found that most symptoms and problems were at their peak 2 or 3 months after the start of treatment[5,12]. A more precisely defined date, for example 2 months after surgery would have been a more appropriate option to compare results between groups.

Between baseline and 6 months after surgery, the change scores of the QLQ-C30 revealed no differences between group I and both pre-fed groups. There were, however, significant differences between group II and III in the functioning scale cognitive functioning and the sympton scale appetite loss.

Table 5 shows mean values of the dimension cognitive functioning of the QLQ-C30. Baseline scores of group II are lower than those of the other groups (without significance) while at six months after surgery, they are approximately the same in all groups. The significant improvement of group II can be explained by a lower baseline score, with a larger ability to improve.

Group III showed a higher level of appetite loss 6 months after surgery. We do not have an explanation for this phenomenon, all the more since the general medical situation regarding nutritional status, immune function markers, postoperative morbidity and survival at this time-point is identical between groups[33]. Both differences reported here may be both related to the small sample of patients in each group that completed the follow-up and to the selection bias that was associated with it: predominantly younger patients and less patients who had been operated for a recurrent tumour after previous radiotherapy, completed the 6 month follow-up period.

Although previous studies report positive effects of arginine supplementation[29,30,34-35,36], such as improved wound healing and immune status, no differences in favour of the arginine supplemented nutrition compared to the standard nutrition could be demonstrated in the QOL questionnaires. However, these studies evaluated physical status rather than QOL, which is a far more complex outcome to assess.

Few studies have evaluated the relation between malnutrition, QOL and head and neck cancer, and these results were found to be contradictory. In one study, malnourished patients scored worse for most functions/items than patients with normal nutritional status, but the differences were not significant[10]. The greatest differences between the two groups were found for physical functioning, global QOL, and role functioning. This is in line with the improvement in physical functioning in both pre-fed groups in our study. Another study reported an increased prevalence of depression among malnourished head and neck cancer patients[37].

More studies have evaluated QOL in head and neck cancer without including the factor nutritional status. In one study, no correlation was found between the patient's self-rated QOL and the severity of the disease[10], while in another study a very high correlation between poor prognosis and low health index/low quality of life was described[38]. Another study examined differences and similarities in QOL of cancer patients with good, medium and poor prognoses, and found that prognosis is only moderately related to physical aspects of QOL, but not to social and psychological aspects[39].

One study found that emotional function in head and neck cancer patients was significantly influenced by the type of surgical procedure, and that long-term survivors reported a high level of disease and treatment related symptoms[8], while another reported significantly better QOL ratings among the 2-year survivors[10]. The authors concluded that QOL measurements may be of prognostic value concerning the survival of head and neck cancer patients. The contradictory findings might be explained by the lack of standardized methods in measuring QOL, which makes it hard to compare results.

Studies comparing QOL in cancer patients and in patients with other diseases, or with healthy control groups, usually reveal surprisingly few and small differences between the different kinds of cancer[40]. Possible explanations for this phenomenon might be that cancer patients get more attention and social support than do healthy people, or that they value life in a different way, and are no longer bothered by most daily hassles.

In this study, we found improvements in some QOL items in the pre-fed groups. Whether this was established by the nutritional support, the extra attention patients got or because of the feeling that something positive was done, is difficult to decide. To explore the issue of extra attention would have required a different study design, with group I receiving as much attention as the tube-fed group, but without the actual feeding or with sham-feeding. This was deemed unfeasible. Perhaps more important is the lack of blinding of patients and health care professionals in group I. Patients who know that they are not tube-fed may indicate lower scores than they might have done in a situation of ignorance of their feeding status.

At the time of this study, there was no EORTC head and neck cancer module. The EORTC Quality of Life Study Group has now developed such a module (the QLQ-H&N35), which is currently being field tested in a larger cross-cultural study involving more than 10 countries[41]. It would be interesting to repeat this study with a larger number of patients, which would allow sub-group analysis in order to identify the impact of diagnosis-specific problems[7,9] on QOL. However, as in this study patients with different tumour localisations were equally divided between groups, and we only used the core questionnaire, which assessed the more general health status of patients, this did not result in a problem to arrive at overall conclusions.

We included the COOP/WONCA charts in this study, because they constitute a brief, practical and valid instrument to assess functional status. In addition, we anticipated that, in the course of time, the patients' health status could decrease to a point where it would no longer be possible to fill out both instruments. In that situation we would have switched to exclusively use the short and very simple COOP/WONCA charts. In practice, however, this situation never occurred. If a generic questionnaire is to be added in this type of studies, the questionnaire needs to be more sensitive to change than the COOP/WONCA charts.

In summary, we found that peri-operative nutritional support has a positive effect on QOL of malnourished head and neck cancer patients in the period preceding surgery. With all patients receiving the same nutritional regimen postoperatively, no benefit of the peri-operative enteral feeding on QOL could be detected 6 months after surgery. No differences in favour of the arginine supplemented nutrition compared to the standard nutrition could be demonstrated. The results suggest that it is recommendable to supply pre-operative enteral nutrition to malnourished head and neck cancer patients because of its positive effect on physical and emotional function, no matter what the effects of this nutritional regimen may be on morbidity and (late) mortality.

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Chapter 8

Summary and conclusions

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Cancer is the second most important cause of death in Western industrialised countries. Many patients suffering from (advanced) cancer present with undesired weight loss, finally leading to cachexia. This is a condition of extreme weight loss that may originate from taste changes, loss of appetite, pain, anxiety, changes in metabolism and side-effects from cancer treatment.

Head and neck cancer patients are, even more than other cancer patients, at high risk of developing malnutrition. First of all, the location of the tumour may lead to swallowing problems and pain upon eating. Secondly, the majority of head and neck cancer patients have a history of alcohol and tobacco abuse and poor dietary habits. Finally, the treatment of advanced head and neck cancer, consisting of extensive surgery with adjuvant radiotherapy, can result in an inability to consume sufficient normal food to meet nutritional requirements.

Surprisingly, malnutrition in head and neck cancer patients is not a subject that has been the focus of systematic study. We hypothesised that malnutrition in this category was largely underestimated and designed the studies as presented in this thesis to establish an objective picture of the true extent of this problem.

Chapter 1

gives a brief review of a wide variety of factors related to malnutrition in head and neck cancer patients. Furthermore, an outline of the thesis is provided.

It is clear from the literature that malnutrition is a common phenomenon in head and neck cancer, but its true extent is difficult to define due to a lack of a universally accepted method of identifying malnutrition. Pre-operative nutrition, designed to prevent complications resulting from the malnourished state, has been shown to benefit some groups of severely malnourished (cancer) patients, but its effect in head and neck cancer has not yet been studied. Many studies have described impaired immune function, both in head and neck cancer and in malnutrition. When patients suffer from both head and neck cancer and severe malnutrition, it remains unclear whether the reported immune dysfunction is a result of the tumour, of the nutritional status or of the combination of both. We hypothesised that correction of the nutritional status by giving pre-operative nutrition, possibly enriched with an immunomodulating nutrient such as arginine, would be of positive influence on postoperative outcome in head and neck cancer patients.

The first part of the thesis is designed to obtain a clear picture of the nutritional status of these patients and the relation between nutritional status and postoperative outcome. The second part describes the results of pre-operative nutritional intervention, with and without arginine, on postoperative complications, survival and quality of life.

Chapter 2

describes the prevalence of malnutrition in a cohort of 64 patients undergoing major surgery for advanced head and neck cancer and its relation with postoperative complications.

To define nutritional status, six well-known nutritional parameters were determined in stable, ambulant patients, one day before surgery. These parameters were: percent weight loss during the past six months, percent ideal body weight, serum albumin, total lymphocyte count, nutritional index (a nutritional risk index based on albumin, percent ideal body weight and total lymphocyte count) and body fat and lean body mass (derived from bioelectrical impedance analysis). Complications were defined as minor, major and non-surgical. Logistic regression was applied as the statistical method to investigate the relationship between nutritional status and complications.

The six different nutritional parameters revealed that the degree of malnutrition was largely dependent on the parameter that was applied. Malnutrition ranged from 20% (based on the results of albumin) to 67% (based on nutritional index). These results confirmed our assumption that there is no single best parameter to define nutritional status.

The results of nutritional assessment were then related to postoperative complications in order to correlate nutritional parameters and outcome in this specific group of head and neck cancer patients. No relation was found between either minor or non-surgical complications and any of the nutritional parameters. A clear statistical relation was found between weight loss during the last six months and the occurrence of major postoperative complications. Approximately 30% of the patients had lost more than 10% weight and the percentage of major complications was calculated to be 65% in this subgroup. In contrast, in well-nourished patients the major complication rate was less then 15%. A marked finding was that patients who had lost >10% of their initial weight still had body weights that were largely within the normal range. Their appearance was usually not one of extreme cachexia. This indicates that absolute body weight and comparison with tables of ideal body weight will be ineffective. It was concluded that head and neck cancer patients having suffered more than 10% weight loss are at increased risk for developing major postoperative complications after major surgery.

In chapter 3

the same 64 head and neck cancer patients were followed for a period of at least three years and the applied pre-operative nutritional parameters were then related to survival, both overall and disease specific. Since patient and tumour characteristics (like lymph node metastases, tumour stage and gender) are known to be of influence on survival, both nutritional parameters and patient and tumour characteristics were analysed by means of the Cox proportional hazards model. The primary goal of this study was to identify the best (combination of) variables predicting survival. None of the investigated nutritional parameters were correlated with survival. When men and women were analysed separately, however, a pre-operative weight loss of > 5% did have a prognostic value for men. It proved to be prognostic for survival, in addition to lymph node stage, surgical margin status and the occurrence of major postoperative complications. Male patients suffering from the combination of pre-operative weight loss and postoperative complications all died within a year and a half of treatment.

Chapter 4

focusses on a selection of immune parameters and nutritional status in head and neck cancer, both in well-nourished and malnourished patients. A variety of immune parameters were measured in 66 head and neck cancer patients (both well-nourished (recent weight loss <10%) and malnourished (recent weight loss ≥10%)) and in 43 healthy controls. The immune parameters included the absolute numbers of leucocytes and lymphocytes, lymphocyte phenotyping and HLA-DR expression on monocytes. Lymphocyte subset populations did not differ between well-nourished and malnourished patients nor between cancer patients and healthy controls. The number of monocytes, however, was increased in both groups of cancer patients, whereas the expression of HLA-DR on these monocytes was diminished in malnourished cancer patients only. A relation between a diminished HLA-DR expression and an increased chance of infection, sepsis and death has previously been reported in the literature. In the light of the high complication rates in malnourished head and neck cancer patients (chapter 2), it may well be that low HLA-DR expression and the associated monocyte deactivation plays a role in the development of these complications.

Chapter 5

describes the results of nutritional intervention in severely malnourished head and neck cancer patients. Forty-nine patients, all of them severely malnourished (with a mean weight loss of ± 15%) were randomized to receive either 1) no pre-operative and standard postoperative tube-feeding, 2) standard pre-operative and postoperative tube-feeding or 3) arginine-supplemented pre-operative and postoperative tube-feeding. Arginine was added because of its reputed effects on immune function and wound healing. Both prefed groups received pre-operative feeding for approximately 9 days. Nutritional targets for tube-fed patients were estimated using the Harris and Benedict equation. The main goals were to study the effects of nutritional intervention on pre-operative changes in nutritional status and on postoperative complications and survival.

Results show that nutritional parameters hardly changed pre-operatively; only albumin decreased in the non-fed group, whereas it stabilised in both prefed groups. No changes in body weight or body composition were noted. Postoperatively, patients in all three groups revealed the same immunological disturbances in response to the operation trauma. Major postoperative complications ranged from 47% to 59% in the three groups and were not different from the data as described in chapter 2. A trend towards an improvement in survival was noted for the patients who received the arginine-supplemented formula. Statistical significance would have been achieved resuming continuation of the trend with n=40 at 3 years.

The results of this study do not support our hypothesis that pre-operative feeding would benefit the severely malnourished patient. No other study has examined nutritionally repletion of patients in a nutritional condition as poor as these patients. Therefore, the results of this study may not be compared with earlier studies. Since no improvements in nutritional status were noted in the nutrition intervention period pre-operatively, it may also be discussed whether the nutritional intervention that we applied was aggressive enough for this category of patients. Moreover, the number of patients studied was relatively small and data indicate that extension of the study would have generated statistically significant results. Finally, it may be hypothesised that the extremely malnourished state of the type of patients studied is not only a result of diminished intake, but especially a manifestation of the endpoint of disease. In that case, the value of nutritional intervention at all can be questioned.

Chapter 6

concentrates on the immune function parameters of the patients presented in chapter 5. Since pre-operative and postoperative immune parameters were not different between the three nutrition intervention groups, results of all patients were pooled and related to survival. The main parameters of interest were HLA-DR expression on monocytes (see also chapter 4) and endotoxin-induced cytokine production. Overall survival was 35%. This is low, compared with the survival rate of a group of both malnourished and well-nourished patients (55%, chapter 3). Analysis of variance revealed that survivors were characterised by less weight loss, a higher HLA-DR expression on monocytes and a higher endotoxin-induced production of TNFα and Interleukin-6 compared with patients who died. For the immune parameters, these observations were most prominent at recruitment into the study, i.e. before any treatment had started. The Cox proportional hazards model identified the existence of co-morbid disease, weight loss >12%, and HLA-DR expression below the cut-off point of 15 (for the mean fluorescence index) to be the parameters with the strongest prognostic influence on survival. Given the poor survival rate in this group of severely malnourished patients, these findings might become of influence in future strategies for deciding whom and how to treat.

Chapter 7

the last chapter, deals with the quality of life of malnourished head and neck cancer patients. This was assessed by two questionnaires: the generic COOP/WONCA charts and the cancer-specific EORTC Quality of Life Questionnaire C30 (QLQ-C30). Results of 31 patients who completed both questionnaires reveal that the COOP/WONCA charts are not specific enough to detect subtle changes in quality of life in this group of patients.

The QLQ-C30, however, showed improvements in physical and emotional functioning in both pre-operatively tube-fed study groups. Whether these results are a positive effect of the extra attention that patients were given or whether they reflect a real improvement, remains unanswered. The fact is that patients did not experience a negative influence of the nutrition, even though this burdened them with a nasal feeding tube.

The conclusions of this study

are that severe malnutrition may be a real threat for head and neck cancer patients having to undergo major surgery with curative intent. Patients with a weight loss of > 10% are at higher risk of major postoperative complications. In addition, malnutrition has a negative influence on survival in male patients.

Of the deficiencies in immune function often accompanying head and neck cancer, HLA-DR expression on monocytes in particular has been found to carry prognostic value.

The treatment of severely malnourished head and neck cancer patients needs more elaboration. The generally accepted treatment of one week of pre-operative nutrition proved not to be sufficient with regard to the prevention of postoperative complications. Survival, however, tended to improve in patients given the nutrition enriched with arginine. A clear beneficial effect was seen in the quality of life of patients who were treated with pre-operative nutrition.
For the future, longer or more aggressive nutritional therapy pre-operatively or the combination of immune modulation and nutritional therapy should be considered in order to restore patients' deficiency in nutrients and depression of the immune system, maybe leading to an improved postoperative outcome.

Nederlandse Samenvatting

Nederlandse samenvatting

In de Westerse geïndustrialiseerde landen is kanker, na hart en vaatziekten, de meest voorkomende doodsoorzaak. Kanker gaat vaak gepaard met ongewenst gewichtsverlies, wat uiteindelijk kan leiden tot cachexie, oftewel extreem gewichtsverlies. Dit kan onder andere ontstaan door smaakveranderingen, gebrek aan eetlust, pijn, zorgen, veranderingen in de stofwisseling en bijwerkingen van de behandeling van kanker.
Bij patiënten met kanker in het hoofd-halsgebied is de kans op het ontstaan van ondervoeding groter dan bij andere patiëntencategorieën met kanker. Dat komt onder andere door de plaats van de tumor. Hierdoor kunnen pijn bij het eten en slikproblemen ontstaan. Daarnaast kennen veel patiënten met hoofd-halstumoren een voorgeschiedenis van slechte eetgewoontes en een overmaat aan alcohol- en nicotinegebruik. Ook de behandeling van hoofd-halskanker, de combinatie van een grote operatie en bestraling, leidt vaak tot blijvende problemen met de voedselinname.
Tot op heden is weinig wetenschappelijk onderzoek gedaan naar ondervoeding bij patiënten met hoofd-halskanker. Met de studies, zoals beschreven in dit proefschrift, is geprobeerd meer duidelijkheid te krijgen over de ernst van het probleem en het voorkomen ervan.

Hoofdstuk 1

Hierin wordt een samenvatting gegeven van een groot aantal factoren die samenhangen met ondervoeding bij kanker in het hoofd-hals gebied.
Uit de literatuur wordt duidelijk dat ondervoeding bij kanker in het hoofd-halsgebied een probleem is. Hoe groot dit probleem werkelijk is, is moeilijk te beoordelen omdat de afzonderlijke studies uiteenlopende methoden gebruiken om ondervoeding te definiëren. Van perioperatieve voeding is aangetoond dat het de kans op complicaties bij ernstig ondervoede patiënten (met kanker) kan verminderen. Bij patiënten met hoofd-halskanker is dit echter nog niet bestudeerd.
Veel studies hebben een vermindering van de immuunfunctie beschreven, zowel in relatie tot ondervoeding als in relatie tot hoofd-halscarcinomen. Het is onduidelijk of de verminderde immuunfunctie bij patiënten met hoofd-halscarcinomen die tevens ondervoed zijn wordt veroorzaakt door de tumor, door de ondervoeding of door de combinatie van beide factoren. Onze hypothese was dat perioperatieve voeding de voedingstoestand van ondervoede patiënten met hoofd-halscarcinomen gunstig zou kunnen beïnvloeden en hiermee van invloed zou kunnen zijn op het postoperatieve beloop van

deze patiënten. Bovendien zou verrijking met arginine, een voedingsstof die van invloed is op het immuunsysteem, een extra positieve bijdrage kunnen leveren.
In het eerste gedeelte van dit proefschrift wordt een beeld geschetst van de voedingstoestand van patiënten met hoofd-halscarcinomen en de relatie met het postoperatieve beloop. In het tweede gedeelte worden de resultaten van voedingsinterventie, al dan niet met arginine, op het postoperatief beloop, de overleving en de kwaliteit van leven beschreven.

Hoofdstuk 2

beschrijft de voedingstoestand van 64 patiënten met hoofd-halskanker die werden opgenomen voor het ondergaan van een grote operatie. Tevens werd hun voedingstoestand gerelateerd aan het optreden van postoperatieve complicaties.
De voedingstoestand werd één dag voor de operatie bepaald bij stabiele, ambulante patiënten. De volgende 6 voedingsparameters werden gebruikt: percentage gewichtsverlies gedurende de afgelopen 6 maanden, percentage ideaalgewicht, serumalbumine, totaal lymphocytengetal, nutritional index (een formule gebaseerd op albumine, percentage ideaal gewicht en totaal lymphocytengetal) en vetmassa en vetvrije massa (afgeleid van de resultaten van bio-elektrische impedantiemeting). Postoperatieve complicaties werden gedefinieerd als klein, groot, of niet-gerelateerd aan de operatie. Met behulp van logistische regressie werd de statistische relatie tussen voedingsstatus en complicaties berekend.
De resultaten laten zien dat de interpretatie van de voedingsstatus sterk afhankelijk was van de parameter die werd gebruikt. Werd albumine gebruikt, dan werd 20% van de patiënten als ondervoed gedefinieerd. Werd daarentegen de nutritional index gebruikt, dan kon 67% van de patiënten geclassificeerd worden als ondervoed. Deze resultaten ondersteunden ons in ons idee dat er niet één voedingsparameter is die als beste gekwalificeerd kan worden.
De zes voedingsparameters werden vervolgens gerelateerd aan postoperatieve complicaties. Er werd geen relatie gevonden tussen de voedingsparameters en kleine of niet aan de operatie gerelateerde complicaties. Er was echter een duidelijke statistische relatie tussen het percentage gewichtsverlies gedurende de voorafgaande 6 maanden en het optreden van grote postoperatieve complicaties. Ongeveer 30% van de patiënten had 10% of meer gewicht verloren en bij deze patiënten was de kans op grote postoperatieve complicaties ongeveer 65%. Bij goed gevoede patiënten was de kans op het optreden van grote postoperatieve complicaties ongeveer 15%. Opvallend was dat ook bij patiënten

met veel gewichtsverlies het lichaamsgewicht meestal nog normaal was, vergeleken met tabellen met ideale gewichten zoals die door verzekeringsmaatschappijen worden uitgeven. Oftewel, zij zagen er niet extreem ondervoed uit. Vergelijking van het lichaamsgewicht met deze tabellen heeft bij deze patiënten dus geen zin.
De conclusie van deze studie was dat patiënten met hoofd-halscarcinomen die meer dan 10% gewicht verloren hebben een verhoogd risico lopen op het optreden van grote postoperatieve complicaties.

In hoofdstuk 3

wordt de situatie van dezelfde 64 patiënten beschreven minimaal 3 jaar na operatie. De 6 voedingsparameters werden gerelateerd aan (ziekte-specifieke) overleving. Omdat bekend is dat lymfkliermetastasen, het stadium van de tumor en het geslacht van de patiënt prognostische factoren zijn voor overleving werden patiënt- en tumorkenmerken tezamen met de voedingsparameters in het statistische model (Cox proportional hazards) geanalyseerd. Het doel van de studie was de beste combinatie van voorspellende parameters voor overleving vast te stellen. In eerste instantie leek geen van de gebruikte voedingsparameters van invloed te zijn op de lange termijn overleving. Toen mannen en vrouwen echter apart werden geanalyseerd bleek 5% gewichtsverlies bij mannen een voorspellende waarde te hebben, evenals lymfkliermetastasen, de status van de snijvlakken bij operatie en het optreden van grote postoperatieve complicaties. Alle mannen die meer dan 5% gewicht hadden verloren èn een grote postoperatieve complicatie hadden gekregen bleken binnen anderhalf jaar na operatie te zijn overleden. Voor vrouwen kon geen voorspellende prognostische parameter worden vastgesteld.

In hoofdstuk 4

wordt de relatie tussen de voedingsstatus en een aantal immuunparameters beschreven bij 66 patiënten met hoofd-halscarcinomen (zowel goed gevoede als slecht gevoede) en bij 43 gezonde mensen (controlegroep). Tot de immuunparameters behoorden onder andere leukocyten, lymfocyten, de phenotypering van lymfocyten en de HLA-DR expressie op monocyten. De subpopulaties van lymfocyten verschilden niet tussen goed gevoede en ondervoede patiënten en evenmin tussen patiënten met kanker en gezonde mensen uit de controlegroep. Het absolute aantal monocyten was echter verhoogd in beide groepen carcinoom patiënten. De HLA-DR expressie op monocyten was verminderd bij de ondervoede patiënten maar niet bij de goed gevoede patiënten. In eerdere literatuur is een relatie beschreven tussen een verminderde HLA-DR expressie op monocyten en een toegenomen kans op sepsis en overlijden. Gehypothetiseerd werd dat het hoge complicatie percentage bij slecht gevoede patiënten met hoofd-halskanker (hoofdstuk 2) samenhangt met de verlaagde HLA-DR expressie en het verminderde functioneren van het immuunsysteem dat daarmee gepaard gaat.

In hoofdstuk 5

worden de resultaten van een voedingsinterventiestudie beschreven. 49 Ernstig ondervoede patiënten (gemiddeld gewichtsverlies ± 15%) werden gerandomiseerd in 3 studiegroepen: 1) de eerste groep kreeg geen preoperatieve voeding en wel standaard postoperatieve sondevoeding, 2) de tweede groep kreeg standaard preoperatieve en standaard postoperatieve sondevoeding en 3) de derde groep kreeg arginine verrijkte preoperatieve en postoperatieve sondevoeding. Arginine werd toegevoegd vanwege de aan deze voedingsstof toegeschreven positieve effecten op de immuunfunctie en wondgenezing. Patiënten in de groepen 2 en 3 werden gemiddeld bijna 9 dagen preoperatief gevoed. De voedingsbehoefte werd berekend met behulp van de Harris en Benedict formule. De studie richtte zich op het effect van voedingsinterventie op de voedingsstatus, op het optreden van grote postoperatieve complicaties en op overleving.
Bij verwerking van resultaten bleek dat de toegepaste voedingsinterventie weinig invloed had gehad op de voedingsstatus. Er werden geen veranderingen in lichaamsgewicht of in lichaamssamenstelling waargenomen. Alleen in groep 1, de niet-preoperatief gevoede groep, daalde het albumine in de periode voorafgaand aan operatie. Na operatie bleek dat patiënten in alle drie de groepen eenzelfde depressie van het immuunsysteem doormaakten. Grote postoperatieve complicaties traden op bij 47% tot 59% van de patiënten. Deze percentages verschillen niet of nauwelijks van het percentage zoals beschreven in hoofdstuk 2. De patiënten in groep 3, de groep met arginine verrijkte voeding, neigden naar een betere overleving. Statistische berekeningen laten zien dat deze trend waarschijnlijk significant geworden zou zijn bij uitbreiding van de studie tot 40 patiënten per groep.
De resultaten van deze voedingsinterventiestudie waren niet in overeenstemming met onze hypothese dat perioperatieve voeding (met arginine) deze slecht gevoede patiënten ten goede zou komen. Daarbij moet echter aangetekend worden dat in geen enkele eerdere studie voedingsinterventie bij patiënten in een dergelijke slechte voedingstoestand is toegepast en dat deze studie dus niet zonder meer te vergelijken is met eerdere studies waarin wel positieve resultaten werden behaald. Aangezien de voedingsinterventie niet leidde tot verbetering van de voedingstoestand, kan de vraag gesteld worden of de interventie wel agressief of langdurig genoeg was. Bovendien moet worden opgemerkt dat het aantal patiënten dat werd geïncludeerd relatief gering was; berekeningen laten zien dat een grotere studie waarschijnlijk wel tot significante resultaten zou hebben geleid. Ten slotte moeten wij ons afvragen of de extreme ondervoeding niet een uiting was van een eindstadium van ziekte en niet puur een uiting van verminderde voedselinname. In het eerste geval kunnen we ons afvragen of voedingsinterventie sowieso wel enige waarde zou kunnen hebben.

Hoofdstuk 6

beschrijft bij de patiënten van hoofdstuk 5 een aantal immuunparameters in relatie tot overleving. Aangezien met betrekking tot de immuunparameters geen verschillen tussen de 3 studiegroepen werden gevonden, werden de resultaten van de 3 groepen samen geanalyseerd. De studie richtte zich met name op de HLA-DR expressie op monocyten (zie ook hoofdstuk 4) en op de door endotoxine gestimuleerde cytokineproductie. De overleving was 35%. Dit is laag, vergeleken met de in hoofdstuk 2 beschreven overleving van 55%. Variantie-analyse wees uit dat de nog in leven zijnde patiënten ten tijde van de studie gekenmerkt werden door minder gewichtsverlies, een betere HLA-DR expressie op monocyten en een hogere endotoxine-gestimuleerde cytokineproductie dan patiënten die overleden waren. Deze resultaten waren voor de immuunparameters het meest duidelijk vóór aanvang van de studie, dus voordat enige behandeling of interventie was ingezet. Met behulp van Cox proportional hazards werden comorbiditeit, een gewichtsverlies van meer dan 12% en een HLA-DR expressie lager dan 15 (gemiddelde fluorescentie index) geïdentificeerd als de parameters met de grootste voorspelbare waarde voor overleving. Gezien de toch slechte overleving van deze ondervoede patiëntengroep kunnen deze parameters in de toekomst mogelijk betrokken worden bij de afweging wie te behandelen en hoe te behandelen.

Hoofdstuk 7

tenslotte, beschrijft de kwaliteit van leven van dezelfde populatie ondervoede patiënten met hoofd-halskanker. De patiënten vulden twee vragenlijsten met betrekking tot kwaliteit van leven in: de algemene vragenlijst COOP/WONCA en de kanker-specifieke vragenlijst EORTC QLQ-C30. De resultaten van de 31 patiënten die beide vragenlijsten invulden wezen uit dat de algemene vragenlijst COOP/WONCA niet specifiek genoeg was om kleine veranderingen in kwaliteit van leven te ontdekken.
De QLQ-C30 liet echter zien dat het lichamelijk en emotioneel functioneren van de

patiënten in de groepen 2 en 3, de beide groepen die voor operatie sondevoeding kregen, verbeterde. Of dit het gevolg is van de voeding of van de extra aandacht die de patiënten kregen, is aan de hand van de resultaten niet te beantwoorden. Duidelijk is in ieder geval dat de patiënten niet oordeelden dat de kwaliteit van leven was verslechterd als gevolg van de sonde in hun neus.

De conclusie van dit proefschrift

is dat ondervoeding een bedreiging vormt voor patiënten die een operatie ondergaan voor hoofd-halskanker. Patiënten met een gewichtsverlies van meer dan 10% lopen een verhoogde kans op het optreden van grote postoperatieve complicaties. Bovendien is aangetoond dat gewichtsverlies bij mannelijke patiënten de kans op vroegtijdig overlijden vergroot.
HLA-DR expressie op monocyten blijkt een immuunparameter te zijn met voorspellende waarde voor overleving.
De voedingsbehandeling van ernstig ondervoede patiënten met hoofd-halskanker behoeft nog verdere uitwerking. De algemeen geaccepteerde behandeling van één week preoperatieve voeding bleek het optreden van grote postoperatieve complicaties niet te kunnen voorkomen. De overleving leek echter te verbeteren als gevolg van de perioperatieve voeding verrijkt met arginine. Patiënten die preoperatief sondevoeding kregen vonden dat dit een positief effect had op hun lichamelijk en emotioneel functioneren.
Voor de toekomst moet langer of agressiever voeden of een combinatie van voeding met immuunmodulatie overwogen worden teneinde de tekorten in nutriënten en de depressie van het immuunsysteem te compenseren. Misschien kan daarmee het postoperatieve beloop worden beïnvloed.

Dankwoord

Dankwoord

Graag wil ik iedereen bedanken die een bijdrage heeft geleverd aan mijn onderzoek en aan de totstandkoming van mijn proefschrift. Enkelen wil ik graag bij naam noemen.

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Prof.dr. S. Meijer, promotor

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Curriculum Vitae

Curriculum Vitae

Maria Anna Elisabeth (Marian) de van der Schueren werd geboren op 30 mei 1962 te Zwijndrecht. Zij behaalde in 1981 haar diploma Gymnasium-β aan de Rijksscholengemeenschap te Tiel. Na de middelbare school werkte ze een jaar als au-pair in de Verenigde Staten.

Van 1982 tot 1986 volgde ze de opleiding Voeding en Diëtetiek aan de Hogeschool van Amsterdam. Tijdens haar studietijd was ze een actief roeister. Met haar boot werd ze onder meer Nederlands kampioen in de categorieën 4-met-stuurvrouw en 8-met-stuurvrouw. Tevens nam zij deel aan het WK roeien voor studenten.

Van 1986 tot 1988 werkte zij als diëtist in het Antoni van Leeuwenhoekhuis in Amsterdam.

Van 1988 tot 1990 vervulde zij een functie als diëtist in het voedingsteam van het Onze Lieve Vrouwe Gasthuis in Amsterdam.

In de voetsporen van prof.dr. R.I.C. Wesdorp vertrok zij in 1990 naar het Academisch Ziekenhuis VU (AZVU), waar zij betrokken was bij de oprichting van het voedingsteam aldaar. In 1993 werden de eerste voorbereidingen getroffen voor het onderzoek zoals beschreven in dit proefschrift. Het onderzoek werd uitgevoerd in de jaren 1994 tot en met 1997. Met dit onderzoek hoopt zij als eerste Nederlandse diëtist op een onderwerp uit het klinisch voedingsonderzoek te promoveren.

In 1998 en 1999 hield zij zich, naast haar werkzaamheden als lid van het voedingsteam van het AZVU, bezig met de verwerking van de onderzoeksgegevens.

Sinds 1999 is zij hoofd van de dienst diëtetiek van het Academisch Ziekenhuis VU.

Zij is getrouwd met Gerbrand van Bokhorst en samen hebben zij twee kinderen, Querijn (5 jaar) en Julie (3 jaar).