Perioperative nutrition in GI cancer patients : assessment of surgical risk, postoperative morbidity and long term survival

Citation for published version (APA):

Meijerink, W. J. H. J. (1992). *Perioperative nutrition in GI cancer patients : assessment of surgical risk, postoperative morbidity and long term survival*. [Doctoral Thesis, Maastricht University]. Rijksuniversiteit Limburg. <https://doi.org/10.26481/dis.19921016wm>

Document status and date:

Published: 01/01/1992

DOI:

[10.26481/dis.19921016wm](https://doi.org/10.26481/dis.19921016wm)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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PERIOPERATIVE NUTRITION IN GI CANCER PATIENTS

**ASSESSMENT OF SURGICAL RISK, POSTOPERATIVE
MORBIDITY AND LONG TERM SURVIVAL.**

Wilhelmus Jan Hendrik Jeroen Meijerink

PERIOPERATIVE NUTRITION
IN GI CANCER PATIENTS

ASSESSMENT OF SURGICAL RISK, POSTOPERATIVE
MORBIDITY AND LONG TERM SURVIVAL.

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Limburg te Maastricht,
op gezag van de Rector Magnificus, Prof.Mr. M.J. Cohen,
volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen
op vrijdag, 16 oktober 1992 om 16.00 uur

door

Wilhelmus Jan Hendrik Jeroen Meijerink

geboren te Hoeven op 27 oktober 1961

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CIP-GEGEVENS KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Meijerink, Wilhelmus Jan Hendrik Jeroen

Perioperative nutrition in GI cancer patients : Assessment of surgical risk, postoperative morbidity and long term survival / Wilhelmus Jan Hendrik Jeroen Meijerink. - [S.l. : s.n.] (Katwijk : Albedon Klop). - Ill.

Proefschrift Maastricht. - Met lit. opg. - Met samenvatting in het Nederlands.

ISBN 90-9005393-X

Trefw.: perioperatieve voeding / postoperatieve complicaties.

Vormgeving en layout : Jeroen Meijerink

Ontwerp omslag : Jeroen Meijerink en Nicole Groenendal

Druk : Albedon-Klop Katwijk

The trial was financially supported by Baxter (Clintec) and Wander Research.
The publication of this thesis was financially supported by Kabi Pharmacia, Clintec and Nutricia.

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De wijsheid, die iemand voor een ander toegankelijk probeert te maken, klinkt altijd als iets dwaas. Wijsheid en wetenschap zijn twee verschillende begrippen. Laten we daarom de wijsheid vergeten en beginnen met wetenschap.

General introduction

1.1 Nutritional assessment and surgical risk

Malnutrition or depletion is associated with an increased incidence of mortality and morbidity of surgical therapy¹⁻⁸. The compromised ability of the depleted patient to cope with the metabolic stress of surgery requires a careful and thorough evaluation of nutritional status in the preoperative period. Assessment of the nutritional status of a patient, is complicated. Objective measurements of preoperative nutritional status commonly used include levels of plasma proteins (total protein, albumin, pre-albumin, gamma globulins, plasma transferrin), delayed cutaneous hypersensitivity skin tests, anthropometric measurements (such as arm muscle circumference, skinfold thickness, weight parameters e.g. actual weight, weight loss, and ideal weight), and body composition measurements (impedance, measurement of total body water).

Most of these parameters are altered by both disease and insufficient food intake. Only very few studies have tried to separate the influence of disease and insufficient food intake on these parameters. In addition, the definition of what is considered an abnormal value of a given nutritional parameter is often based on the erroneous concept that alterations in these parameters are the sole result of insufficient food intake. Whether the separation of influence of disease and insufficient food intake has any practical implication is difficult to appreciate. This has led to a widely varying incidence of malnutrition in all sort of patients reported in the literature. However, most studies indicate a high incidence of malnutrition of patients on admission in a general hospital⁹⁻¹².

Nutritional status parameters alone do not effectively identify patients which are at risk for developing postoperative complications. Many studies showed in monofactorial analyses significant associations between individual parameters of nutritional status and postoperative outcome. Several (nutritional) indices obtained by means of multivariate analyses were proposed to predict morbidity and mortality better (Chapter 4). Unfortunately, such data are not of sufficient precision to be used for the individual patient, because they are affected by several patient related factors such as hydration, stress and prior starvation.

1.2 Perioperative nutritional support.

The acknowledgement that an impaired nutritional status has an adverse effect on outcome of disease and therapy has contributed to the development of artificial nutrition. Much effort has been put in the assessment of the efficacy of nutritional support. The benefit of nutritional support, either by the parenteral or by the enteral route, in the perioperative management of the depleted cancer patient, is still under debate. The causes for this controversy will be discussed in chapter 3 & 4.

1.3 Study population

Cancer patients form an appropriate group to study the effects of depletion on postoperative outcome as well on the potential benefit of preoperative nutritional intervention. Anorexia, obstruction, increased energy expenditure, taste alterations, etc. leading to depletion, are common features in cancer disease. Therefore, this group of patients should, on theoretical grounds, benefit from preoperative nutritional intervention. However, tumor-host relationships are different between types of cancer and interfere with trial results if all kinds of cancer are included. Nonetheless, in literature most trials used miscellaneous types of cancers.

We, therefore, chose to select a homogeneous cancer patient group. Gastro-intestinal cancer patients form a proper study population because tumour behaviour and characteristics are comparable, gastro-intestinal cancer has a high incidence in western countries, and above mentioned metabolic aberrations will occur in an early stage in this type of cancer. All these reasons lead to a rapid intake of depleted cancer patients in the study.

The incidence of gastric cancer in western countries is between 5 and 10 new cases per 100.000 per year^{13,14}, with a predominant incidence in males^{15,16}. Adenocarcinoma is the most frequent malignant tumor of the stomach; it comprises 97% or more of these lesions¹⁶. Survival in most gastric cancer series is limited. Eighty-five percent of patients at time of diagnosis are surgical candidates^{16,17}. Half of these 85% will undergo 'curative' resection with a 5-year survival rate of approximately 25%¹⁷. The other half will undergo palliative surgery with no long term survival¹⁷. Overall survival at 5 years is between 5 - 10 percent^{16,17}.

In Western countries cancer of the colon and rectum ranks second after lung cancer in incidence of new cases and death rates^{13,16}. The incidence varies in

Western countries between 25 and 60 new cases per 100.000 population per year^{13,14}. Males and females are equally affected. The incidence increases with age, beginning to rise at age 40 and reaching a peak at 75-80 years^{16,18}. Primary therapy consists of surgery^{13,16}. About 10% is inoperable at time of diagnosis¹⁶. One-third will undergo a palliative resection with less than 5% 5-year survival. After 'curative' resection 5-year survival is about 40%. Overall 5-year survival is between 25-30%^{13,14,19}.

1.4 Aims of the study

The aim of this study was to investigate in a randomised trial the effects of perioperative nutritional support, given by either the parenteral or enteral route, on the incidence of postoperative morbidity and mortality in depleted patients undergoing surgical treatment of a gastric, colon or rectal malignancy.

Secondary goals in this clinical trial were:

1. to identify factors which are significantly associated with postoperative morbidity and mortality of gastric and colorectal cancer surgery.
2. to identify parameters which are associated with long term survival of gastric and colorectal cancer treatment.
3. to investigate whether perioperative nutritional support results in improvement of long term survival of gastric and colorectal cancer patients.

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Methodological considerations

2.1 General aspects: trial design

The trial was designed as a sequential trial to compare three groups stratified for the most relevant patient factors¹. A sequential trial design was chosen because of ethical reasons: it would allow termination of the trial after performance of an interim analysis if one of the treatments would have a clear advantage or if it was unlikely that prolongation of the trial would result in a significant difference between trial arms.

2.2 Number of patients required

To estimate the number of patients necessary for an adequate answer on the trial objection and to estimate the expected duration of the trial, a postoperative major morbidity rate of 30 % in depleted cancer patients was assumed. A reduction of 20 % of major morbidity was regarded to be of clinical significance. Alpha (the chance to reject incorrectly the statistical null hypothesis of no difference) was set to 5 % and beta (the chance to detect a reduction of 20 % of major morbidity) was set to 95 %. On this basis a total of ± 80 patients per study arm was required to obtain an answer in a 2-tailed χ^2 -test.

The percentage gastrointestinal cancer patients with signs of depletion was expected to be 60 % of all admitted patients with a gastrointestinal malignancy. It was expected that upto 20 % of the patients were not eligible for operation because of the stage and condition of the patient (inoperability), or because of the age of the patient (patients over 80 years were excluded from randomisation). This implied that without a significant improvement in morbidity in one of the treatment arms in an interim analysis, a total number of about 500 patients was required ($80 \times 3 \times 100/60 \times 100/80 = 500$).

2.3 Duration of the trial

With an admittance rate of ± 100 patients per year (96 in 1982) to the University Hospital Maastricht, the expected duration of the trial was 4 - 5 years. If results of the interim analysis would show a statistical benefit for the treatment arm, the

trial was to be discontinued. Also, if the interim analyses would indicate no difference between control and treatment arms, this too would be a reason to discontinue the trial.

2.4 Study protocol

2.4.1 Patients

The effect of perioperative nutritional support was prospectively studied in consecutive patients admitted to undergo major surgical therapy for newly detected and histologically proven gastric, colon or rectal cancer. The procedure was defined by non-emergency laparotomy for curative or palliative surgical therapy for gastric or colorectal cancer.

Specific exclusion criteria were:

- a contraindication for delaying surgery for 10 days
- a contraindication for parenteral or enteral nutritional support
- over 80 years of age.

All excluded patients were monitored for their postoperative clinical course and they were included in the risk factor analysis (Chapter 5). Informed consent was obtained from all participating patients.

2.4.2 Nutritional assessment

Because it was considered ethically unjustified to subject patients that had a normal percentage ideal body weight (PIW), plasma albumin (Alb) and total lymphocyte count (TLC) to nutritional intervention, these patients were excluded from randomisation. In 1985 we computed an index³ consisting of parameters which distinguished patients that on clinical grounds were judged to be nutritionally depleted, from a healthy control group by the next formula:

$$(0.14 \times \text{Alb (gr/l)}) + (0.03 \times \text{PIW (\%)}) + (0.73 \times \text{TLC (10}^9\text{/mm}^3\text{)}) - 8.90$$

In the current study all patients who had a value below the mean of the reference group (1.31) in the original study of de Jong³ were randomised. This is an arbitrary choice, resulting in inclusion in the trial of patients in the grey area between absence and presence of depletion. Within this area it is difficult to draw strict limits.

Non-depleted patients were excluded from randomisation. They served as non-depleted control group. These patients were operated without delay within 2 - 3 days after admission to the hospital.

2.4.3 Stratification

Patients with an index below 1.31 were stratified for age, tumor localisation, and weight loss.

-tumor localisation	-gastric cancer -colon or rectal cancer
-weight loss	-< 15 % -≥ 15 %
-age	-< 65 years -≥ 65 years

2.4.4 Randomisation

The patients with a value below the cut-off point were after stratification for tumor localisation, age and weight loss, randomised to receive perioperative total parenteral nutrition (TPN), preoperative enteral nutrition (TEN), or to serve as depleted controls. Patients in the control group were operated without delay, within 2 - 3 days. Patients who refused after randomisation to participate in one of the nutritional supported trial groups, were analysed according to the intention-to-treat principle. They also were operated without delay.

2.4.5 Surgical procedures

Surgical procedures preformed were

- gastro-enterostomy
- gastric tumor resection with anastomosis
- entro-enterostomy without tumor resection
- entro-enterostomy with tumor resection
- colon resection with end colostomy
- low anterior resection

2.4.6 Data collection

Blood was sampled preoperatively from all patients according to protocol to determine hematological parameters, electrolyte status, protein parameters. Preoperative anthropometric evaluation included determination of weight, height, weight loss during the preceeding year, and percent weight loss (Appendix 1). Weight loss was obtained by standard dietary evaluation by a registered dietitian. Percent ideal weight was calculated using the Metropolitan Life tables¹.

Peroperative blood loss was estimated and recorded by the anaesthesiologist, duration of the surgical procedure was recorded from the anaesthesiology report. Tumor stage was scored according to the TNM-classification (Appendix 2).

Postoperative complications were scored until hospital discharge. They were categorised as absent, minor or major complications. Mortality was total, in hospital mortality from any cause.

Complications related to the insertion of a central venous catheter, technical or septic, metabolic complications related to the parenteral nutritional support, or metabolic and mechanical complications related to the enteral nutritional support were scored separately.

2.4.7 Nutritional support

Preoperative nutritional support, both parenteral and enteral, was planned to contain 150% basal energy expenditure (BEE) calculated with the Harris-Benedict formula⁴ as non protein calories and to last at least 10 days.

2.4.7.1 Parenteral nutrition

T.P.N. solutions were prepared in the hospital pharmacy according to current standards. Basis solutions contained 7 gr nitrogen per liter (Synthamin 14^R), 25 % glucose per liter. Intravenous lipid emulsions were administered at least 3 times weekly (500 ml Intralipid^R 20 %). Vitamins (MVI^R) and trace metals (zinc, copper, manganese, selenium, chromium, and iodine) were supplemented daily. Electrolytes (potassium, sodium, magnesium, calcium, chloride, phosphate) were supplemented according to the individual patient's needs.

Postoperative parenteral nutrition was continued in the T.P.N. group until patients were able to take 120 % BEE orally.

2.4.7.2 Enteral nutrition

Enteral nutrition, (Precitene^R N or Isotein^R (N:kcal ratio 1:92, protein 107 gr/l, 1575 kcal/l)), was administered by naso-gastric tube or orally. Postoperatively the patients resumed oral nutrition as tolerated .

2.4.7.3 Control patients

Patients in the depleted control group and in the non-depleted reference group were planned to undergo surgery without delay. Normal preoperative care was given according to the planned procedure e.g. bowel lavage. In the postoperative phase patients in these groups, as in the enteral group, were allowed increasing amounts of liquids and solids as tolerated. Only in the event of a major postoperative complication parenteral nutrition was started on indication.

2.5 Analysis of results

2.5.1 Complication analysis

All patients in the trial groups were analysed according to the intention-to-treat principle. Data were summarised as means and standard deviations in each outcome group. Groups were compared on continuous parameters using ANOVA and Scheffé's post hoc t-test⁵. After categorisation using clinically accepted cut-off points, Mantel-Haenszel chi-square tests⁶ were applied to test the association of parameters with outcome (scored as 1, 2, 3 for no, minor, major complications).

The association of several parameters simultaneously with outcome was assessed with a continuation-ratio multiple logistic regression model^{7,8}. In these analyses the occurrence of a complication and the occurrence of a major complication, given any complication, were taken as dependent variables. We assumed the same parameters to be explanatory for both, unless the coefficients were significantly different.

P-values smaller than 0.05 were considered significant.

2.5.2 Survival analysis

Survival was measured from date of the surgical procedure. Survival analysis included the in hospital postoperative mortality. The medical records of all patients were reviewed to assess survival and cause of death till may 1991. The general practitioner was called for information on the actual status of the patient when the patient was lost to surgical outpatient follow-up or when the last attended control at the surgical outpatient clinic was longer than 2 months prior to last follow-up date.

Survival was analysed using the Kaplan-Meier method⁹, for all patients as well as for subgroups. The survival curves of groups of patients were compared using the log-rank test¹⁰. The efficacy of perioperative nutrition and prognostic potential of nutritional parameters, adjusted for effects of the other riskfactors was tested using a Cox (proportional hazards¹¹) regression model. This regression model included all preoperative parameters which appeared to be important in the log-rank analyses, and the nutritional support parameters.

P-values smaller than 0.05 were considered significant.

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An assessment of nutritional depletion and surgical risk

3.1 Introduction

The effectivity and validity of nutritional assessment methods are still uncertain. There are several reasons for this uncertainty. In the past it has been proposed that it is possible to determine solely by means of nutritional assessment, which patients are at risk for postoperative complications. Furthermore, nutritional assessment methods have often focused on (a decreased) nutritional intake. Finally, parameters for nutritional state and indicators for surgical risk are frequently used as equivalents, because 'malnourished' patients often have a less favourable outcome of therapy.

It is the purpose of this chapter to analyse which factors can cause depletion of a patient and how these factors are related with other factors traditionally thought to influence the outcome of therapy.

When patients are metabolically stable, body composition is kept constant over longer periods of time through maintenance of a balance between intake and losses of energy, protein, and other essential nutrients. Deficiencies are the result of a derangement of the balance, either on the intake side or on the expenditure side, and lead to changes in body composition and disturbed organ functioning.

Nutritional assessment signifies detection of abnormal body composition and organ function resulting from *insufficient nutritional intake*; including energy and protein intake, and also intake of other essential nutrients.

However, the actual intake of energy, protein and other nutrients by depleted patients is not always decreased. Some studies in cancer patients revealed a normal food intake compared to a control group^{1,2}. Therefore, nutritional assessment in these depleted patients becomes metabolic assessment. Nutritional assessment under these circumstances is used to detect abnormal body composition and disturbed organ function resulting from *increased loss*: increased energy expenditure, increased protein degradation, increased loss of total body nitrogen, and increased loss of essential nutrients. In most cases a mixture of both conditions is present.

As a result of abnormal body composition and the ensuing disturbed organ

function the response to the presence of disease or trauma may become impaired. Abnormal body composition and organ function therefore impose additional risks to the patient, but are not synonymous to the development of complications of disease, or the outcome of the treatment of disease.

This chapter intends to sort out the responses of several parameters of body composition and organ function to:

- impaired intake of energy and protein
- increased losses of energy and protein
- a mixture of both derangements

Furthermore, the relationship of abnormal parameters with the response to disease and trauma will be described.

The ultimate goal is to estimate which improvements nutritional support can have on the response of the patient to disease and trauma.

3.2 Starvation experiments: impaired intake.

Under normal circumstances food intake is adapted to changing needs, regulated by sensation of hunger, which depends on factors such as the amount of energy expenditure in work, climatological circumstances, and the nutritional value (energy content) of nutrients¹. After uptake of nutrients in the absorptive phase directly after a meal, in the post-absorptive phase glucose levels are maintained within a rather narrow range. In this phase the brain is still largely dependent on glucose, but other tissues, particularly skeletal muscle, become increasingly dependent on free fatty acids, mobilised from adipose tissue. Plasma free fatty acids levels are rising^{4,7} and liver glycogen is falling and nearly depleted after 24 - 48 hours⁸. Gluconeogenesis becomes increasingly significant, so that after 24 hours of abstinence of caloric intake gluconeogenesis is the prime contributor of hepatic glucose production⁹. Early fasting is accompanied by lower insulin levels and elevated glucagon levels, provoking hepatic glycogenolysis and hepatic gluconeogenesis, supported by release of nitrogenous substrates, mainly glutamine and alanine, from skeletal muscle¹⁰. These lower plasma insulin concentrations are also of influence on fat metabolism. Insulin is a potent antilipolytic hormone. A fall in insulin levels make long chain fatty acids the most important source of energy during prolonged starvation, thus preserving muscle mass.

It has been demonstrated that a healthy person can withstand prolonged starvation without any damage to the individual. Benedict¹¹ showed in a healthy volunteer during a 30 day fast a progressive decrease in oxygen consumption, indicating a corresponding decrease in energy expenditure. Even total food

abstinence over a period lasting more than two months by Irish political detainees was survived by 33 out of 43 prisoners⁹. Russel¹² demonstrated in anorexia nervosa patients that prolonged decreased intake, extending over a mean of 4.3 years, resulted in slightly decreased serum albumin values, with normal lymphocyte counts and a creatinin-height index within normal ranges. Total body weight, lean body weight and percent body fat were decreased.

Thus, a decreased intake of energy, protein and other nutrients without concomitant disease shows a gradual decrease of body weight and energy expenditure with substantial loss of body fat mass and relative preservation of lean body cell mass.

3.3 Disease status: increased loss.

Damage of tissues, irrespective of the cause (infection, malignancy, surgery, trauma, and especially sepsis), is accompanied by changes in glucose and lipid metabolism, an increased net protein degradation, resulting in increased losses, hypermetabolism, and a negative nitrogen balance¹³. These injuries alert central nervous systems, via afferent neural impulses¹⁴. This arousal of the central nervous system results in activation of autonomous nervous and neuroendocrine systems¹⁴, with elevation of the so-called stress hormones (cortisol, glucagon and catecholamines¹⁵).

In muscle, a decline in net amino acid (AA) uptake and an increase in muscle degradation occurs. In the splanchnic region, glutamine (GLN) and alanine (ALA) uptake are increased¹⁶. The net liver AA uptake increases, probably caused by an increased hepatic protein synthesis, ureagenesis and gluconeogenesis. This gluconeogenesis and the concomitant peripheral glucose resistance contributes to hyperglycemia¹³, commonly observed during trauma and sepsis.

The glucocorticoid hormones seem to be the key regulators of the accelerated intestinal protein metabolism that occurs following surgical stress¹⁷. During stress states, an elevation of arterial corticosteroid concentration causes an increased net gut GLN uptake, and a net glucose, ALA, and ammonia release from the gut¹⁸ and possibly spleen. The intestinal release of ALA supports hepatic gluconeogenesis, while ammonia is converted to a large extent to urea, excreted by the kidney and thus contributing to the negative nitrogen balance associated with stress¹⁷.

The hypermetabolic state, which often accompanies major trauma, is not only coupled with an elevation of the stress hormones, but also with a (temporary) elevation of cytokines (e.g. TNF, IL-6)¹⁹. It is very likely that these cytokines

moderate the changes in metabolism, observed in trauma and/or sepsis. It is as yet uncertain whether their release is proportional to the amount of circulating stress hormones, and how the elevated cytokine levels are influenced by the catabolic condition.

Patients with septicemia, episodes of fever, and trauma show increased loss of energy and protein, decreasing weight parameters^{20,21} and decreasing plasma albumin^{20,22,23} levels. The cancer-bearing-state is often accompanied by increased losses, which in some types of cancer can be caused by a hypermetabolic state resulting from an increased basal energy expenditure²⁴. Thus, disease is in general associated with alterations in intermediary metabolism, hormonal changes, and probably changes in cytokine levels. They play a (major) role in depletion, although their relationship is not yet fully understood.

Disease state and especially the septic state is accompanied by rapidly falling plasma total protein and albumin concentrations, decreasing lymphocyte counts, and rapid changes in electrolytes and trace elements. This may demonstrated best in (healthy) young trauma patients at the Intensive Care Unit with signs of sepsis where these changes occur within few days.

3.4 The combination of impaired intake and increased loss.

In most cases a mixture of starvation and increased loss exists. The recognition of depletion having a nutritional origin and a metabolic origin may also explain why nutritional intervention is not always succesful in reversing ongoing 'malnutrition'. The possible origin of impaired 'nutritional' status and, therefore, the impaired capability to respond to intrusions, may have either a nutritional origin (a result of food intake of insufficient quantity or suboptimal quality), or may have a metabolic origin (a result of metabolic alterations) (figure 3.1). Both result in depletion. As the term 'malnutrition' acknowledges

Figure 3.1

only the nutritional origin, the term depletion reflects more accurately than the term 'malnutrition' the clinical condition we seek to describe. The metabolic side of depletion is probably not easily reversed with 'ordinary' nutritional intervention. This may explain why for example the depleted patient with Crohn's disease having ongoing septicemia or chronic infection, cannot recover from his depletion by means of nutritional intervention, as long as the underlying disease (the active inflammation with the metabolic and hormonal changes) is not cured. The patient, depleted to a similar degree, with stenosis of the bowel as result of Crohn's disease without active inflammation, will recover rapidly after nutritional intervention has started²⁵.

By assuming both nutritional and metabolic factors as cause of depletion the fact is acknowledged that the response to an intrusion is not exclusively dependent on the nutritional status of the subject, but rather on the integrity of body composition and organ function. Thus, by including the causes of depletion in the assessment of depletion, not only those groups that need additional nutritional therapy may be identified, but it may also become possible to predict the effect of nutritional therapy.

3.5 Abnormal parameters: relation with response to disease.

The goal of the assessment of the presence of depletion is to identify patients that are unable to stage a normal response to a disrupting factor (trauma, operation, infection). These patients carry an additional risk for development of complications of their disease or of the treatment of their disease. Depletion is one of the risk factors for outcome of therapy, be it surgical therapy, chemotherapy, or radiation therapy. The outcome of therapy is a result of several factors e.g. patient related factors (age, coexisting diseases), treatment of disease, or disease itself, together with depletion (figure 3.1).

This view differs from usual definitions of 'nutritional status' or malnutrition in this respect that these definitions assume 'nutritional status' to be impaired if associated with morbidity and mortality. This approach assumes impaired 'nutritional status' to be the only determinant of the development of morbidity and mortality, and denies the role of other factors in this process. This has led to overestimation of the importance of 'nutritional status' as determinant of the outcome of disease or treatment of disease. If one accepts that the development of morbidity and mortality of chemo-, radiation or surgical therapy is dependent on the magnitude of the trauma itself, and the capability of the host to respond to the trauma, the poor results of nutritional support trials designed to decrease morbidity and mortality can be explained. The capability to stage a response is

only in part dependent on 'nutritional status', and nutritional support can, therefore, only partly influence or modify this response.

Many individual parameters have been suggested to describe depletion and the degree of malnutrition. In monofactorial analyses these parameters showed a fair to good correlation with the incidence of postoperative complications. But no single indicator has been proven superior to any other. Several studies demonstrated that single abnormalities in nutritional parameters tend to lose their discriminatory capacity, because very few patients display normal values for all parameters used^{20,26-29}. In the individual patient these parameters were not very useful in predicting the occurrence of complications. Combination of parameters does not always increase sensitivity, reliability and applicability for the individual patient because of the high degree of correlation among variables. Therefore, several investigators developed indices, combining multiple parameters of anthropometric, biochemical, and immunological measurements. These indices were based on multiple variate regression analyses. One of the problems of these methods is that they consider only parameters, that were traditionally thought to be associated with malnutrition. As a consequence this has led to overemphasis of the nutrition related risk factors. In addition, it gradually became clear that some of the parameters used to identify impaired 'nutritional status', rather demonstrate the presence of metabolic stress²². Furthermore, considerable confusion has been created because many authors defined 'nutritional status' parameters as abnormal only on the basis of their association with the development of complications.

Finally, the relative importance of 'nutritional status' was - indirectly - shown to be small, because trials investigating the effect of nutritional intervention on outcome of for example surgical therapy, almost invariably failed to demonstrate a benefit (chapter 4).

The emphasis on the role of 'nutritional status' parameters as risk indicators has distracted the attention from the role that disease and treatment, i.e. surgery, related factors have in the development of postoperative outcome. To our knowledge there are no studies that combine depletion parameters with non nutritional status related risk factors, which are traditionally found to be responsible for the postoperative outcome of surgical therapy, aimed at determination of the additional risk that originates from depletion.

Originally most interest was directed towards parameters that were considered to be objective measurements of an impaired 'nutritional status' or 'malnutrition'. Generally accepted parameters for nutritional assessment are total protein, transferrin, albumin and pre-albumin, alone^{22,30} or in nutritional

indices^{20,26-29,31-33}, parameters identifying muscle mass and fat stores, creatinin-height index, muscle function tests, immunological status, and weight and weight loss^{20,21,30,34-37}. Many of these parameters show a significant correlation with postoperative morbidity and mortality^{20,26-28,31,34,35,38-47}, and are therefore often used to calculate the risk for development of postoperative complications^{20,21,26,28,31,34,35,39}.

Age⁴⁸⁻⁵¹, extent of surgical procedures or any other disease treatment, peroperative blood loss and transfusion^{20,52,53}, and individual coexisting diseases have been studied much less frequently for their relation with outcome.

Weight loss and weight relative to ideal weight are parameters that have been used successfully by many authors to identify patients at risk for the development of (postoperative) complications^{54,55}. In 1936 Studley⁵⁶ already reported weight loss as prognostic factor for postoperative outcome. Weight loss is a simply obtained indicator, with a high reliability when obtained by standard dietary methods by registered dieticians, and is of value when it is combined with clinically obvious impairment of organ function²¹.

Transferrin and albumin have half lives of 10 and 20 days, respectively. Plasma levels of these proteins therefore change slowly in response to alterations in nutritional intake^{57,58}. They decrease very quickly, however, in response to trauma⁵⁹ (including elective surgery), myocardial infarction⁶⁰, sepsis⁶¹, and severe illness⁵⁸. These changes are caused by inter-compartmental fluid shifts, alterations in vascular permeability⁶², and changes in rates of synthesis and degradation⁶¹. Therefore, albumin has been claimed a parameter of disease instead of being a nutritional parameter²². Despite this, serum albumin concentration is the most widely used single indicator of surgical risk.

There have been several attempts to increase the predictive value of nutritional parameters. Combinations of various parameters were presented as nutritional indices or risk indices, mostly being the result of multivariate stepwise regression analyses. Again, the assumption was made that malnutrition is synonymous to increased risk. However, the effort to improve the methods to define malnutrition by combining parameters, did not result in improvement of the predictive value for postoperative complications because these two terms are not equivalent. Increasing the predictive value of indices for postoperative complications is only then possible, if other factors, also related with postoperative complications, are considered too. Such factors are age, coexisting diseases, extent and duration of surgical procedure and peroperative blood loss, anesthesia technique, and skill of the surgeon.

3.6 Combination of parameters

A summary of combinations of 'nutritional' parameters as they have been proposed in the literature is presented below.

In 1979 the Prognostic Nutritional Index (PNI)^{32,63-65} was presented by Mullen et al.:

$$\text{PNI (\%)}: 158 - (16.6 \times \text{Alb}^*) - (0.78 \times \text{TSF}) - 0.20 \times \text{TFN} - (5.8 \times \text{DH})$$

Seltzer⁶⁶ proposed the Instant Nutritional Assessment (INA), based on 2 parameters:

$$\begin{array}{ll} \text{INA: Malnourished when either} & \text{Alb} < 3.5 \text{ g/100 ml} \\ & \text{or} & \text{TLC} < 1500 \text{ } 10^6/\text{mm}^3 \end{array}$$

Harvey et al.⁶⁷ presented the Hospital Prognostic Index (HPI):

$$\text{HPI}: (0.91 \times \text{Alb}) - (1.00 \times \text{DH}) - (1.44 \times \text{sepsis}) + (0.98 \times \text{diagn}) - 1.09$$

Baker et al.^{68,69} made the clinical judgement essential part of the index, called Subjective Global Assessment (SGA):

SGA: normal nutritional status/mild-/severe malnutrition to be determined on information obtained from a careful history on intake, weight loss, underlying disease, and functional status and physical examination of anthropometric parameters.

Gassull et al.⁷⁰ combined the outcome of 3 parameters: TSF, MAMC, Alb.

De Jong et al.⁷¹ compared a group of healthy people with a group of patients considered malnourished on clinical grounds, as established by experienced clinicians. This Nutritional Index (NI) indicated the clinical impression of malnutrition:

$$\text{NI}: 20.68 - (0.24 \times \text{Alb}) - (19.21 \times \text{Pre-Alb}) - (1.86 \times \text{TLC}) - (0.04 \text{ PIW})$$

* Alb = plasma albumin (g/l), TSF = triceps skin fold (cm), TFN = transferrine (mmol/l), DH = delayed hypersensitivity (response 1-3), TLC = total lymphocyte count ($10^6/\text{mm}^3$), MAMC = mid-arm muscle circumference (cm), Pre-Alb = plasma pre-albumin (g/l), PIW = percent ideal weight (%), FeBC = iron binding capacity $\mu\text{g/dl}$.

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Perioperative nutritional support: a trial review

4.1 Introduction

Many trials investigating the effect of nutritional support on the incidence of postoperative complications have been performed in patients undergoing surgical therapy for malignant disease. The reason to focus on cancer patients is the relatively high incidence of depletion in these patients. Depletion is an important risk factor, especially in patients undergoing major gastrointestinal surgery (chapter 3).

The depleted state of gastrointestinal cancer patients has often many reasons e.g. mechanical obstruction of the GI tract, diagnostic procedures necessitating patients to be starved repeatedly, disease related factors resulting in a disruption of the balance between energy intake and expenditure, and alterations in food intake regulating mechanisms. Depletion in these patients reduces the tolerance to a surgical trauma and may lead to a (severely) catabolic state aggravating postoperative complications (chapter 3).

Nutritional support during the perioperative period may restore body reserves and functions, and thereby decrease morbidity in patients who undergo surgical procedures. Preoperative nutritional support has been claimed to induce improved woundhealing^{1,2}, decreased incidence of wound infections³, respiratory insufficiency⁴, septic complications^{4,9}, less weight loss¹⁰⁻¹⁵, improved nitrogen balances^{6,16-20}, improved serum protein parameters^{6,8,10,11,14,21,22} and increased lymphocyte counts^{8,18,22}.

However, the effect of preoperative parenteral nutrition on postoperative outcome has been tested in only a few properly designed comparative trials.

4.2 Trial prerequisites

The organisation and set-up for clinical trials investigating the effect of perioperative nutritional support should fulfill certain criteria.

To avoid patient selection, the study should have a prospective randomised design. Comparison with historical or matched control groups harbours the danger of a selection bias and endangers a correct interpretation of results. To

avoid a selection bias the study should include all eligible patients fitting the descriptive criteria of the study population, and the study should clearly define exclusion criteria. Both inclusion and exclusion criteria must be mentioned in the patients and methods section, when a trial is reported. After randomisation, the non-treatment control group should be operated at once. Presenting control patients with a normal hospital diet, during the same period prior to surgery as the patients receiving preoperative artificial nutrition without careful registration of actual intake may overestimate the intake of these patients: they often suffer from a decreased appetite while, in addition, diagnostic procedures often prohibit the use of food during significant parts of the day.

Inclusion of a non-depleted control group results in the possibility to evaluate the complication rate that is the result of the treatment procedures used, without the additional effects of an impaired nutritional status.

Nutritional status parameters should identify a patient group that is relevant. With 'relevant' we imply that the patient group that is selected carries a, preferably proven, additional risk for the development of postoperative complications. In addition, only depleted patients are to be subjected to randomisation, because it is not ethically justifiable to subject patients who have a normal body weight, no weight loss, normal plasma protein levels, normal values of parameters of immunological functioning to nutritional therapy. These non-depleted patients should therefore be excluded from randomisation.

The trial should be stratified for factors which have a significant association with the outcome of the treatment. Stratifications should include tumor localisation if more malignancies are to be included; age, because of association of age with increasing numbers of coexisting diseases; and severity of the impairment of the nutritional status. Each of these factors may contribute to outcome and should therefore be controlled for in the randomisation of patients.

Advance calculations (power analysis) should result in patient groups of sufficient size to reach significance of the expected differences. Interim analyses are necessary to avoid treatment which has already been shown to be inferior to the other treatment.

A complete material and methods description should include the statistical analyses used, making comparisons between studies possible.

One relevant evaluation criterium should determine the trial goal, becoming the basis for the statistical calculations. Evaluation criteria may include minor and major morbidity, and mortality, where both minor and major complications need accurate definitions.

It is crucial to supply sufficient and adequate nutrition to the patients in the treatment arm(s). Calculation of the amount of energy may be based on a calculation of basic energy expenditure with the help of the Harris-Benedict

formula²³, or on measured energy expenditure using a ventilated hood system²⁴. When reporting the results of a study, the composition and the amount of the nutritional support administered must be mentioned.

It is beyond discussion that the daily care of central venous catheters and administration of nutritional support are routine procedures for participating surgeons and nurses, making it a safe procedure.

4.3 Review

In the English literature at least 53 retrospective or prospective trials have been published, most of them between 1976 and 1982. These trials were published mainly in surgical journals. Several trials have been published more than once with minor or major adaptations of the text, but seemingly including the same patient groups.

Of these trials on pre-operative and postoperative nutritional support, 15 were published as abstracts^{7,8,13,18,22,25,34} or as a letter³⁵ to the editor.

Twenty of the trials included only cancer patients^{6,10,12,14,15,17,36-38}, while 17 trials included patient groups with both malignant and benign disease, or trauma patients^{3,4,9,15,16,20,37,49-59} (Table 4.1).

We investigated whether these 53 studies fulfilled the criteria described earlier in this chapter.

Nine studies^{4,37,40,43,46,50-52,55} involving parenteral nutritional support did not have a prospective randomised design including a control group. Intervention and control patient groups were compared and matched for several clinical and biochemical parameters, and sometimes a comparison with historical control groups was made.

A 'normal', i.e. non-depleted patient group that can serve as a reference group, is scarcely included^{10,38,58}.

Six trials^{12,20,45-47,55,57,59} comparing parenteral and enteral nutritional support did not include control groups without nutritional support. Whether preoperative nutritional support has a beneficial effect on the outcome of these patients cannot be assessed from these trials.

Table 4.1: Overview of trials: perioperative nutritional support trials

author (reference)	trial set-up	n	outcome criteria	TPN/ TEN n	nutritional support days		only MN patients	preop. regimen	control group	regimen control patients	preop. days controls	remarks	results
					preop.	post							
Askenazi (40)	retrospective and only postoperative TPN	35	length of hospitalisation	22	no	?	no	1.3-1.6 BEE 0.28-.04g N	yes	400 kcal/day	as normal	radical cystectomy, 2 deaths in control group	significant reduction of hospitalisation
Smale (37)	retrospective non- randomised TPN	159	complications	54	>6	?	no	>35 kcal/kg/day >1.5 g protein	yes	?	as normal	patients retrospectively assigned to low or high risk group depending on index	in high risk patients reduced morbidity
Clark (52)	retrospective non- randomised TPN	70	major septic - complications ¹	26	>5 or	>5	no	?	yes	? some TPN >5 days postop	as normal	mixed population	trend towards lower septic complications
Mullen (4)	retrospective non- randomised TPN	145	complications	50	?	?	no	>35 kcal/kg/day 1.5 g prot/kg/day	yes	? most had postop TPN	as normal	variety of diseases, retrospective assignment by a prognostic index	in high risk patients reduced morbidity
Daly (43)	retrospective non- randomised TPN	244	complications ¹	72	>5	?	yes	45 kcal/kg/day 1-2 g prot/kg/day	yes	?	?	all patients with esophageal cancer from 1960-1980; patients before 1973 no TPN	reduced complication rate in patients with preop. TPN
Starker (50)	prospective non- randomised TPN	59	complications ¹	59	?	?	yes	150% BEE 1.5-2.0g N/day	no			heterogeneous patient group	complication rate depen- ding from response to TPN
Collins (51)	prospective non- randomised TPN	30	weight nitrogen skin folds, complications	20	no	?	no	AA infusion 0.23g N/kg/day or 0.23g N/kg/day + 35kcal/kg/day	matched			variety of diseases	improvement of postoperative parameters
Yeung (55)	TPN vs TEN not randomised	28	body composition	14/ 14	?	?	no	±42 kcal/kg/day	TEN elemen- tal diet	±36 kcal/kg/day	?	heterogeneous patients groups	no difference in body composition

Bower (20)	TPN vs TEN randomised postoperative	20	lab values	10/ 10	?	>7	no	1000-3000 kcal/day N?	NCJ*	1000-3000 kcal/day N?	as normal	GI or pancreatico-biliary surgery	TEN more effective compared to TPN
Adams (59)	TPN vs TEN randomised postoperative	46	N-balance complications ²	23/ 23	no	mean 22±24	no	170-200% BEE	jejunos- tomy	190-220% BEE	no	multiple trauma patients	equal effective
Heylen (45)	TPN vs TEN randomised postoperative	20	nutritional parameters	10/ 10	no	8	no	2400kcal/day 16g N/day	NCJ*	same as TPN	?	total gastrectomy	equal effects
Lim (12)	TPN vs TEN randomised perioperative	24	complications, albumin nitrogen, weight	12/ 12	>21	?	no	60-65 kcal/kg/day 0.18-0.28g N/kg/day	gastro- tomy	same as TPN	as TPN	oesophageal carcinoma	TPN more affective compared to TEN
Sako (41)	randomised postoperative TPN	69	complications	34	no	?	no	?				mainly postoperative TPN support	no significant reduction
Fasth (3)	randomised postoperative TPN	92	complications	48	no	>7	no	45 kcal/kg/day 0.2 g N/kg/day	yes	16 kcal/kg/day dextrose 10%	?	stratification for colorectal cancer and inflammatory bowel disease	no significant reduction
Allison (15)	randomised postoperative TPN	122	complications ¹	?	no	<6	no	?	yes	saline	?	no patient description	no differences
Yamada (44)	randomised postoperative TPN	69	immune functions	11	no	18	no	2000 kcal/day	no	?	?	gastric cancer	restored cell mediated immunocompetence prolonged survival
Moore (54)	Non randomised postoperative TEN	26	complications ¹ serum proteins	12	no	7-20	no	?	yes	?	?	abdominal trauma patients, reoperation or dying <5 days excluded	TEN less septic abd. complications, improved serum proteins

author (reference)	trial set-up	n	outcome criteria	TPN/ TEN n	nutritional support days		only MN patients	preop. regimen	control group	regimen control patients	preop. days controls	remarks	results
					preop.	post							
Sagar (53)	randomised postoperative TEN	30	weight N-balance	15	no	?	no	1000-1600 kcal/day	yes	500-1000 kcal/day	?	major GI operations, patients not described	less negative N-balans shorter hospital stay
Muggia (56)	randomised postoperative TEN	15	N-balance, weight serum proteins	8	no	?	no	?	yes	matched for isonitrogenous/ isocaloric amounts	?	variety of GI operations	no difference observed
Delaney (40)	randomised postoperative TEN	115	?	19	no	4-40	no	1800-2700 kcal/day	no	-	?	esophageal and gastric cancer	?
Haffjee (47)	postoperative TPN	15	N-balance	15	?	21	yes	3700 kcal/day 20g N/day	no	-	-	esophageal cancer	positive N-balans
Goode (57)	preoperative TPN	8	?	8	?	?	yes	10-12 N/day	no	-	-	Crohns disease	repletion of lean tissue mass
Thompson (38)	TPN perioperative randomised trail	41	weight serum albumin complications ¹	12	>5	>8	yes	2000-4000 kcal/day	yes	?	?	GI cancer, reference group WL>101b	no reduction of complications
Bellantone (49)	TPN perioperative randomised trail	100	septic complications	49	>7	?	yes	30 kcal/kg/day 0.2 g N/kg/day suppl. to diet	yes	?	?	GI surgery, ⁹ exclusions in TPN group	in high risk patients reduced complications
Bellantone (9)	TPN perioperative randomised trail	?	septic complications	?	>7	?	yes	30kcal/kg/day 0.2 g N/kg/day suppl. to diet	yes	? normal diet	?	patients classified in 3 groups by 3 different indices. Overlap of patients? GI surgery	in all groups reduction of complications by TPN
Holter (10)	TPN perioperative randomised trail	84	complications ¹ serum albumin	30	3	>10	yes	±2000kcal/day ±80 g prot/day	yes	?, blood, albumin	?	referencegroup WL<101b, trail group WL>101b	no reduction by TPN

Moghissi (17)	TPN perioperative randomised trail	15	weight N-balance	10	5-7	6-7	no	34-36 kcal/kg/day 0.18-0.2g N/kg/day	yes	6 kcal/kg/day dextrose/saline	?	esophageal cancer, no staging of tumor, high exclusion rate in control group (n=5)	positive N-balance in TPN
Jensen (42)	TPN perioperative randomised trail	20	complications ¹ hospital stay	10	2	6	no	40-5- kcal/kg/day 1.5-2.0 g AA	yes	5% glucose/saline	?	rectal cancer	significant reduction of hospital stay
Megiud (39)	TPN perioperative randomised trail	66	complications ¹	32	>9	?	no	40 kcal/kg/day 0.3 g N/kg/day	yes	?	3,5	variety of GI cancer	less complications in the TPN group
Heatley (36, 48)	TPN perioperative randomised trail	74	complications ¹	38	7-10	?	no	40 kcal/kg/day 0.2 g N/kg/day suppl. to diet	yes	normal diet ± 3000 kcal 15g N	?	gastric and esophageal cancer	significant less wound infections in supported groups
Preshaw (16)	TPN perioperative randomised trail	47	colonic anastomosis	24	1	5	no	50g fat, 70g prot. 350-700g glucose	yes	?	?	mixed pathology, colonic resection, refusals	no difference excluded before
Mueller (6)	TPN perioperative randomised trail	125	complications ¹	66	10	?	no	45 kcal/kg/day 1.5g prot/kg/day	yes	normal diet ±2400 kcal?, N?	?	variety of cancer, stratification for nutritional status and tumor site	significant reduction of major morbidity and mortality by TPN
Mueller (14)	TPN perioperative randomised trail	171	complications ¹	112	10	?	no	45 kcal/kg/day 1.5g prot/kg/day	yes	normal diet ±2400 kcal?, N?	8,3	wide variety of cancer patients	reduction of complications by TPN
VA-trail (58)	TPN perioperative randomised trail	459	complications ¹	192	0-16 mean 7,9	?	yes	1000 kcat above REE, oral ad lib	yes	normal diet ad lib. ±1280 kcal (0-3342 kcal)	>3	wide variety of diseases many exclusions from a potentially large group	reduction of complications in severely depleted patients

1 complications not or poor defined

2 regimen depending from preoperative response of serum albumin

3 total of 14 days of nutritional support

4 NCJ: needle-catheter jejunostomy

Thirteen of the randomised trials^{12,17,20,38,42,45,47,51,53-57} included too few patients to achieve enough statistical power to evaluate clinical outcome. Instead, several smaller trials^{40,42,51,53,54} claimed significant improvements, especially of nutritional status parameters, i.e. weight gain^{12,51,57} and nitrogen balance^{12,17,47,51}. Whether these improvements were associated with decreased morbidity, the ultimate goal of perioperative nutritional support remained uncertain.

Whereas some randomised trials were of adequate size, the perioperative nutritional support given must be considered inadequate, varying from 1 day preoperative¹⁶, 3 days preoperative¹⁰, 5 - 7 days preoperative¹⁷ to only post-operative nutritional^{3,15,41,44,46,53,54,56} support. This approach does not allow adequate repletion of body reserves and restoration of body functions.

Six of the remaining randomised perioperative trials^{9,10,16,36,38,49}, report either an inappropriate nutritional regimen or define poorly the quality of the nutritional support given. Only the VA-trial⁵⁸ supplied sufficient parenteral nutrition between 7 and 15 days preoperatively.

Some trials supplied the control group with a normal hospital diet^{6,9,14,36}, however, without an adequate check of the actual food intake. Other trials did not define food intake^{10,16,38,39,49} nor the preoperative hospital stay of the control group^{6,9,10,16,17,36,38,39,42,49,58}.

A trial becomes clinically relevant if it gives an answer to the question whether surgery should be delayed to allow adequate nutritional repletion or that surgery should be performed shortly, two or three days, after admission of the patient. A trial investigating the efficacy of preoperative nutritional support should compare these two realities in clinical practice. Comparing nutritional support with a control group of patients that is left in the hospital without attention for their food intake will result in a comparison of a patient group undergoing starvation with a group receiving nutritional support.

As it is unlikely that patients in a non-depleted condition will benefit from preoperative nutritional support only depleted patients should be included in a trial.

Eight prospective randomised trials^{6,14,16,17,36,39,42,49} did not exclude well nourished patients.

Although thirteen studies^{6,10,14,15,36,38,39,42,43,50,52,54,59} defined a reduction of complication rate as trial goal they did not, or poorly, state what kind of complications or definitions of complications were used to score outcome.

A prospective randomised trial of sufficient size to generate a statistically

significant answer to the question whether perioperative nutritional support is able to reduce (major) postoperative complications, and which meets all above mentioned criteria has only been performed once⁵⁸.

4.4 Meta-analyses

The awareness of the fact that most trials showed major or minor shortcomings has led to the pooling of trial results and performance of meta analyses.

Brennan⁶⁰ reported 7 trials of TPN as an adjunct to surgery^{10-12,17,18,36,41} (including one orally presented trial), of which one study was reported twice^{10,11} and one as an abstract¹⁸. All but one⁴¹ reported positive effects of parenteral nutrition in reducing morbidity and mortality.

Buzby et al.⁶¹ reviewed 8 trials^{6,10-13,17,18,36} performed before 1982, 2 reports presenting the same study, 2 studies reported as abstracts. They concluded that results of these studies did not allow any answer, because the reports were incomparable.

Klein et al.⁶² reviewed the literature of 28 studies on parenteral nutrition and cancer therapy. Perioperative nutritional support in cancer surgery was the subject of 11 trials^{6,10-13,18,32,36,38,41,42}. In this meta analysis two papers report on the same study¹⁰⁺¹¹, and three studies are reported as abstracts^{13,18,32}. The authors concluded that preoperative TPN may be effective in patients with gastrointestinal tract cancer, where it appears to reduce major surgical complications (pooled $p=0.01$) and operative mortality (pooled $p=0.02$).

The meta analysis of Detsky et al.⁶³ included 18 trials (23 references) available up to 1986 of perioperative nutrition and surgery^{4,6,10-12,16-18,25,27,32,36,37,38,41,43,51,64-68}. Five times a study was presented twice^{10+11,25+36,27+68,51+67,4+37}, and 4 studies were reported as an abstract^{18,25,27,32}. The authors concluded that routine use of preoperative parenteral nutrition is not justified; however, this intervention may be helpful in subgroups of patients who are at high risk, defined as patients severely depleted before having surgery, patients who develop complications that are expected to result in prolonged periods (at least 10 - 14 days) of ileus and inadequate nutritional intake, and patients undergoing surgery that results usually in prolonged periods (at least 10 - 14 days) of inadequate nutritional intake.

Meguid et al.⁶⁹ reviewed in more detail 3 parenteral nutritional support studies

including control groups^{16,44,51}, and 3 enteral nutritional support vs control group⁵³⁻⁵⁵ studies. These authors concluded that both ways of nutritional intervention are equally effective in providing nutritional support. Compared with control patients they found the provision of postoperative nutritional support to be effective in improving or maintaining nutritional status. They concluded that correction of malnutrition, either before initiating therapy whenever possible or concomitant with treatment when necessary, is very likely to be beneficial.

Jensen⁴² reviewed 6 trials on pre- and postoperative nutritional support^{6,10,17,36,38,51} and 2 trials in which enteral nutrition is compared with parenteral nutrition^{12,41}. He concluded that nitrogen balances and plasma protein parameters improved, while weight gain was found in the parenterally supported group. No difference was found between enteral and parenteral nutrition in these respects, and both may decrease postoperative morbidity and mortality, which, according to the authors, may not be limited to depleted patients.

Table 4.2 shows the references used in these reviews. Most reviews use the same studies as a reference. The references that are used three times or more are listed in table 4.3. This table also lists the most important criteria that trials should fulfill. The studies of Mueller⁶, Heatley³⁶, and especially the Veterans Administration-trial⁵⁸ are according to our criteria the most complete studies. Major criticisms on those two first mentioned trials are that non-depleted patients were not excluded from randomisation and that the control group did not undergo surgery within a few days after admission, being left on a normal hospital diet, sometimes without adequate control of this intake. In the study of Mueller control patients stayed in the hospital as long as patients in the intervention group did, while the study of Heatley is not clear on this point.

Points of concern in the VA-trial are that patients admitted for elective minor surgery as well as cancer patients undergoing extensive thoracic and abdominal surgery are included. Criteria that designate patients 'malnourished' are rather mild. Omitting patients with concurrent illness may have induced some bias. The presumed reduction of major complication rate with 50% reflects too high expectations of the effects of perioperative nutrition. Nevertheless, the VA-trial is the best performed trial on perioperative nutrition till now.

The results are furthermore difficult to interpret because of a wide variety of diseases in the trials. Some trials use depleted cancer patients, while others look at major operations regardless of the underlying disease. Some trials evaluate

Table 4.2: References used in the trial reviews

author	references
Detsky	10 11 20 21 22 24 25 26 28 43 45 46 47 49 57 59 60 61 62 63 64
Klein	11 20 21 22 23 25 44 47 49 57 58
Buzby	11 20 21 22 23 25 44
Brennan	20 21 22 24 25 44 57
Meguid	43 45 73
Jensen	11 20 22 24 43 44 49 57

Table 4.3: Analysis of trials cited at least 3 times in the reviews

Author	Prospective	Compl	Suff. n	Pre nutr	MN	Contr	Cancer
Mueller	yes	no	yes	yes	no	yes	yes
Holter	yes	no	no	no	yes	yes	yes
Holter	yes	no	marginal	no	yes	yes	yes
Lim	yes	yes	marginal	yes	no	no	yes
Moghissi	yes	no	no	no	no	yes	yes
Simms	abstract						
Heatly	yes	no	marginal	yes	no	yes	yes
Sako	yes	yes	marginal	no	no	yes	yes
Collins	yes	yes	no	no	no	yes	no
Thompson	yes	no	no	no	yes	yes	yes
Prospective : Prospective randomised							
Compl : Complications well defined							
Suff n : Sufficient patients in trial							
Pre nutr : Sufficient preoperative nutrition							
MN : Only malnourished trial patients							
Contr : Inclusion of control group							
Cancer : Cancer patient population							

only superficial wound infections or minor complications, others major morbidity. In addition, an adequate definition of a complication is only rarely included.

All studies supplying more than 7-10 days of preoperative nutrition claimed an improvement of the postoperative course for all patients or high risk subgroups of patients^{4,9,14,37,39,49,50}, albeit that only in a few trials significant results are obtained^{6,36}.

We conclude from this trial review that the trials performed to date, show minor or major shortcomings with regard to design, execution and reporting of the results.

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Risk factors for postoperative complications in gastric and colorectal cancer patients

5.1 Abstract

In the past two decades much emphasis has been placed upon the relation of preoperative 'nutritional status' parameters and outcome of surgical therapy. However, a combined evaluation of depletion parameters with other factors implicated in the development of postoperative complications has scarcely been performed.

In a prospective study the relation of depletion parameters in addition to parameters of preoperative health status and parameters of the extent of the surgical trauma with the incidence of postoperative complications was investigated.

One hundred seventy two patients (63 female, 109 male) admitted to undergo surgery for recently detected gastric ($n=45$) or colorectal carcinoma ($n=127$) participated in this study. Perioperative blood loss ($p<0.0001$) and age ($p<0.05$) were significantly associated with the incidence of postoperative complications, whereas anthropometric parameters of nutritional status were significantly associated with the severity of the complications ($p<0.05$). Although plasma albumin was associated with the development of postoperative complications, this relation disappears after correction for the aforementioned parameters. Other factors, e.g. hemoglobin, total protein, pre-albumin, duration and type of procedure, surgical skill, and coexisting disease showed no significant association with postoperative outcome.

5.2 Introduction

The presence of depletion, resulting in the loss of body cell mass, is associated with impaired cell function and therefore with impaired tissue and organ function (Chapter 3). The relation of the presence of depletion with impaired outcome of a surgical trauma is not clear. If depletion indeed has an independent, significant, influence on the outcome of a surgical procedure, depletion would be an attractive focus for improvement. If nutritional support effectuates

in improved tissue and organ functioning, and consequently in improved outcome of surgical trauma, the magnitude of these improvements are depending of the impact of depletion on outcome of surgical trauma. This idea has been the basis of the concept of perioperative nutritional support.

Studies trying to evaluate the role of depletion in the outcome of surgical trauma, mostly only evaluate parameters describing depletion. Many individual depletion parameters showed in monofactorial analyses a fair to good correlation with the incidence of postoperative morbidity and mortality¹⁻¹⁷, and were, therefore, often used to calculate the risk for development of postoperative complications^{2,7,14,16,18}. No single indicator has been proven better than any other^{5,7,16,19}. To improve the predictive value of parameters in the individual patient combinations of parameters were suggested. Indices, derived from multiple variate regression analyses, combining anthropometric, biochemical, and immunological measurements, did not show increased sensitivity, reliability and applicability for the individual patient because of the high degree of correlation among variables (Chapter 3).

One of the problems of the previous analyses is that they consider only parameters, that are traditionally thought to be associated with depletion. As a consequence this has led to overemphasis of the nutrition related risk factors. In addition, it gradually became clear that some of the parameters used to identify impaired 'nutritional status', rather demonstrate the presence of metabolic stress²⁰. Furthermore, considerable confusion has been created because many authors defined 'nutritional status' parameters as abnormal only on the basis of their association with the development of complications (Chapter 3).

The emphasis on the role of nutritional status parameters as risk indicators has distracted the attention from the role that disease and surgical procedure related factors have in the development of postoperative complications. To determine the additional risk that originates from an abnormal nutritional status, we analysed prospectively preoperative nutritional status parameters, in addition to other well accepted surgical risk factors, for their association with postoperative complications. Such risk factors include type and duration of the surgical procedure, surgical skill, peroperative blood loss, type and stage of the disease, age of the patient, preoperative hemoglobin, and coexisting diseases.

5.3 Patients and methods

5.3.1 Patients

The relation of nutritional status parameters in addition to parameters of preoperative health status and parameters of the extent of surgical trauma with the incidence of postoperative complications was prospectively studied in patients admitted to undergo surgery for recently detected gastric and colorectal carcinoma. Patients with preoperative nutritional support were excluded. Postoperative nutritional support was started only if a major complication had occurred, or starvation had continued more than 7 - 10 days.

5.3.2 Study design and parameters

Blood was drawn preoperatively from all patients to determine hemoglobin, white blood cell count, total lymphocyte count (TLC), total protein, albumin, pre-albumin, transferrin, electrolyte status, creatinin and urea. Preoperative anthropometric evaluation included determination of weight, height, weight loss during the preceding year, and percent weight loss (PWL). Percent ideal body weight (PIW) was calculated using tables of the Metropolitan Life Insurance Company²¹. Perioperative blood loss, duration and type of surgical procedure were recorded.

5.3.3 Complications

Postoperative complications were monitored until hospital discharge or death. Postoperative complications were recorded as absent, minor or major complications (Table 5.1).

5.3.4 Surgical skill

Surgery was performed by senior staff surgeons, junior staff surgeons and senior residents in the presence of a senior or junior staff surgeon. Surgical procedures that were performed included:

- gastro-enterostomy
- gastric tumor resection with anastomosis
- entero-enterostomy without tumor resection
- entero-enterostomy with tumor resection
- abdominal-perineal rectum resection with end colostomy
- low anterior (rectum) resection

Tabel 5.1: Complication definition

MINOR	
Wound infection	Clinical aspect, positive culture or necessity for surgical drainagex
Urinary tract inf.	Positive culture $>10^7$ micro-organisms/ml urine
Pulmonary tract inf.	positive sputum culture, abnormal chest X-ray requiring treatment with antibiotics.
MAJOR	
Respiratory insuff.	Ventilatory assistance for > 12 hrs. postoperative or mechanical renewed ventilation after detubation.
Cardiac insuff.	Clinical and radiological diagnosis requiring cardiotonics and/or diuretics, or myocardial infarction confirmed on ECG or by serum enzyme elevations.
Renal insuff.	Plasma urea levels elevated by 50 % or a plasma creatinin elevation with 20%.
Intra-abd. abscess	Purulent fluid collection, demonstrated by ultrasound, or CT-scan guided drainage or at reoperation.
Fistula	Diagnosis on clinical grounds or proven by fistulography.
Anastomotic leakage	After clinical or radiological diagnosis, necessity for operation or drainage.
Wound dehiscence	Dehiscence of the wound requiring surgical closure.
Sepsis	Positive bloodculture, persisting temperature above 39° C., associated with hypotension and hypoperfusion.
D.I.C. syndrome	Positive FDP-test, abnormal clotting tests and decreasing thrombocyte counts.
Mortality	Any postoperative in-hospital mortality.

5.3.5 Statistical analysis

Data were summarised as means and standard deviations in each outcome group. Groups were compared on continuous parameters using ANOVA and Scheffé's post hoc t-test²². After categorisation using clinically accepted cut-points, Mantel-Haenszel chi-square tests²³ for linear trend were applied to test the association with outcome (scored as 1, 2, 3 for no, minor and major complications).

The association of several parameters simultaneously with outcome was assessed with a continuation-ratio multiple logistic regression model^{24,25} (SAS). In this analysis the very occurrence of a complication (minor or major), and the occurrence of a major complication, given any complication, were taken as dependent variables. We assumed the same parameters to be explanatory for both, unless the coefficients were significantly different. P-values smaller than 0.05 were considered significant.

5.4 Results

5.4.1 Patients

One hundred and seventy two patients (63 female, 109 male) entered this study. In 45 patients gastric cancer and in 127 patients colorectal cancer was recently detected. The mean age was 67 years. The patients had normal mean values of hematological and biochemical parameters, a mean ideal body weight of 102%, a mean weight loss of 6%, and a mean blood loss of 840 ml during the surgical procedure with a mean duration of 3 hours (Table 5.2).

Eight patients received postoperative parenteral nutritional support because of major complications (mean 21.3 days, range 8 – 63).

5.4.2 Complications

An uncomplicated postoperative course was observed in 93 (54.1%) patients. Minor complications occurred in 49 (28.5%) patients, and major complications, including mortality (n=11), in 30 (17.4%) patients. Significant differences between groups were observed for preoperative plasma albumin levels, percent ideal body weight and percent weight loss, duration of surgical procedure and peroperative blood loss (Table 5.2). No significant differences were observed for age, preoperative hemoglobine, total protein, and pre-albumin values, total lymphocyte count. Also type of surgical procedure, tumor stage or tumor site showed no significant differences between groups (Chi-square >0.1) (Table 5.2).

5.4.3 Surgical skill

No difference was found in complications between senior staff surgeons, junior staff surgeons or senior residents supervised by a qualified surgeon. All procedures were performed in equal numbers by the three surgeon groups.

Table 5.2: Analysis by presence of complications

	Overall	No	Minor	Major	p
	mean (range)	mean (SEM)	mean (SEM)	mean (SEM)	anova
Age (years)	67 (39-88)	66 (1.11)	68 (1.76)	71 (1.98)	ns
Haemoglobin (mmol/l)	8.1 (2.6-1.11)	8.2 (0.16)	8.1 (0.22)	7.6 (0.33)	ns
Lymphocyte count (10 ⁶ /ml)	1.89 (0.3-5.4)	1.95 (0.07)	1.93 (0.08)	1.61 (0.17)	ns
Total protein (g/l)	71 (52-98)	71 (0.68)	72 (1.18)	69 (1.01)	ns
Albumin (g/l)	36 (21-47)	36 (0.48)	36 (0.68)	33 (0.80) ⁺	0.05
pre-albumin (g/l)	0.24 (0.05-0.44)	0.25 (0.01)	0.25 (0.01)	0.21 (0.01)	ns
Percent ideal weight (%)	102 (62-138)	103 (1.32)	107 (1.97)*	93 (2.55) ⁺	0.0001
Percent weight loss (%)	6 (-2.2 -35.3)	5 (0.66)	5 (0.74)*	9 (1.43) ⁺	0.01
Duration of procedure (hr.min)	3.06 (0.45-7.15)	2.52 (0.11)	3.24 (0.22)	3.04 (0.18)	0.05
Peroperative blood loss (ml)	840 (0-6000)	588 (91.5)	828 (162.7)*	1633 (241.8) ⁺	0.0001
Posthoc t-test (Scheffé) * p <0.05 vs minor + P<0.05 vs no					

Procedures in gastric or colorectal cancer patients, stage of disease, nutritional status were also equally distributed over the three surgeon groups. Also there was no correlation between experience of the surgeon and duration of operative procedure, peroperative blood loss, or duration of postoperative hospital stay of the patients.

5.4.4 Age

Thirty one patients were over 80 years (mean 82.8, range 80-88, 4 gastric and 27 colorectal cancer). Because advanced age is associated with impaired health status, this subgroup of the study population was analysed separately (Table 5.3). Diabetes mellitus was more frequently observed in the older patients. An abnormal ECG was frequently present, but none of the patients with preoperative ECG abnormalities suffered from postoperative cardiac complications.

Table 5.3: Comparison of patients under and over 80 years of age

	< 80 yrs (n=141)	>80 yrs (n=31)	p
D.M.	6 (4.2%)	5 (16.1%)	0.05
Abnormal ECG	21 (14.9%)	13 (41.9%)	0.01
PIW < 95 %	31 (22.0%)	13 (41.9%)	0.05
PWL % (mean)	5.9	7.5	ns
Pre-albumin < 0.20 g/l	51 (36.2%)	17 (54.8%)	0.01
Duration > 3 hrs	70 (49.6%)	7 (23.0%)	0.01
Mortality	7 (5%)	4 (13.0%)	ns
TLC < 1.25 l/mm ³	19 (13.5%)	12 (46.0%)	0.001

Chronic G.I.-tract diseases, chronic obstructive pulmonary diseases (COPD) and neurological diseases were not more frequently present in the older age patients. Perioperative blood loss in patients over 80 years was not different from that in patients under 80 years of age. Hemoglobin (7.0 vs 8.3 mmol/l), total protein (67 vs 71 g/l), and albumin (33 vs 36 g/l) values were decreased compared to values in patients under 80 years, albeit not significantly. Ideal weight, pre-albumin values and lymphocyte counts were significantly decreased.

Surgical procedures were shorter in patients over 80 years compared to those performed in patients below 80 years.

Mortality did not differ significantly: 4 out of 31 (13.0 %), as compared to 7 out of 141 (5.0%) in the group below 80 years ($p=0.1$).

5.4.5 Coexisting diseases

In this study 6 patients suffered postoperatively from major pulmonary complications requiring special medical care. The age of all 6 patients was over 60 years, 4 were older than 70 years. Three of these patients had pre-existent C.O.P.D. and all 3 died of respiratory failure (Table 5.4). Forty eight patients had a history of cardiac disease, 23 patients complained preoperatively of coronary insufficiency, and 37 showed preoperative ECG aberrations. Six of these patients suffered major complications (3 deaths), while 13 patients suffered minor complications. None of the deaths was due to cardiac failure.

Table 5.4: Association of coexistent diseases with the development of post-operative complications.

	n	no	minor	major	p
D.M.	11	6	4	1	ns
Hepatic diseases	1	1	-	-	ns
Renal diseases	3	2	-	1	ns
Coronary complaints	23	14	8	1	ns
Myocardial disturbances	34	15	13	6	ns
Neurological diseases	19	10	7	2	ns
Chron. G.I. tract disease	29	19	6	4	ns
C.O.P.D.	24	11	5	8	ns
Corticosteroids	4	-	1	3	0.01

Two patients suffered myocardial infarctions postoperatively although they had no history of cardiac complaints. Both patients suffered from postoperative sepsis, had lost a large amount of blood peroperatively, were operated for stage IV carcinoma, and were using corticosteroids preoperatively. However, none of the above associations was significant, as was the case with other preexisting diseases.

In contrast, the use of corticosteroids was significantly associated with post-operative complications ($p < 0.01$). All 4 patients using steroids preoperatively suffered postoperative complications, 3 of them suffered major complications, while 2 patients died.

5.4.6 Multivariate analysis

To exclude effects of confounding factors a multiple logistic analysis with complication rate as dependent factor was performed. Factors not showing significant independent association with postoperative complications were removed step by step, provided the removal of a factor did not cause a large shift in the coefficients of the remaining factors.

Peroperative blood loss was associated with postoperative complications at a high significance level (table 5.5). In addition, age was significantly associated with postoperative complications.

To determine which factors showed an independent association with progression of a complication from minor to major, the severity of the complication was analysed as a second dependent variable. Once a complication occurred not only blood loss, but also percentage ideal weight and duration of the surgical procedure were significantly associated with the severity of the complication.

Table 5.5: Multivariate analysis

	CHI-SQ	p
Development of any complication		
Duration of procedure	0.43	ns
Blood loss	15.79	0.0001
P.I.W. (%)	0.03	ns
Age	5.07	0.05
In case of occurrence of a complication		
Duration	4.61	0.05
P.I.W. (%)	6.98	0.01
Age	3.23	ns

Results of a stepwise (logistic) multivariate analysis with factors used as linear variables. The upper part of the table shows the factors which are associated with the development of any complication, the lower part the factors associated with the severity of a complication.

5.5 Discussion

The identification of a factor as a surgical risk factor largely depends on what factors in literature are analysed for their association with postoperative complications. In addition, it depends on which population is studied and to what specific surgical trauma the patients are exposed. Most studies concerning determination of surgical risk have focussed on 1 or 2 (groups of) factors. Thus, weight, ideal weight and weight loss^{2,3,6,18,26,27}, plasma total protein and albumin alone²⁸ or in nutritional indices^{5-7,14,16,19,29}, age³⁰⁻³², extent of surgical procedures, peroperative blood loss and transfusion^{6,33,34}, and many individual coexisting diseases have been studied for their relation with postoperative complications. For each of these factors or groups of factors a significant association with postoperative outcome has been demonstrated (Chapter 3).

However, an integration of depletion parameters and other known risk factors to show the relative value of the individual or grouped parameters has not been published.

The broad interest in the field of nutrition has resulted over the past two decades in a considerable number of publications, demonstrating that aberrations of nutritional status parameters are risk factors for surgical outcome. The attractiveness of the (strong) association of nutritional status with postoperative complications has always been the suggestion that an impaired nutritional status

can be treated, in contrast to many other risk factors.

This has led to high expectations of the ability of nutritional intervention to decrease morbidity and mortality from surgical therapy. These expectations were, as we know now, too high. Firstly it gradually became clear that most of the parameters used to identify impaired nutritional status, rather demonstrate the presence of metabolic stress³⁰. Secondly subsequent trials investigating the effect of nutritional intervention on outcome of surgical therapy, almost invariably failed to demonstrate a benefit.

The results of our study suggest that the extent of a surgical procedure, as reflected by blood loss and duration of the procedure, and age, are associated with the development of postoperative complications. Apart from these factors, parameters of nutritional status, as reflected by weight loss and percent ideal body weight, are associated with the severity of the occurring complication. Parameters reflecting the presence of metabolic stress, e.g. albumin, did not show an independent association with the development of postoperative complications.

We found no difference in complications, morbidity or mortality of procedures performed by senior staff surgeons, junior staff surgeons, or senior residents supervised by a staff surgeon. In the literature conflicting data have been reported on this subject. Some authors claim increased morbidity in surgical procedures performed by residents³⁵, where it is not clear if they were assisted or supervised by staff surgeons. Others report a higher incidence of complications in procedures performed by senior staff surgeons correlating with hospital stay and need for postoperative nutritional support⁶. The results of the latter study can be explained by the fact that more experienced surgeons perform the more difficult procedures. Difficult procedures show a correlation with factors such as duration of procedure, need for blood transplantation and postoperative nutritional support. This illustrates the relation of these factors and the difficulty to interpret the results. This association can also be explanatory for the lack of a positive correlation between experience and complications in our study or even a negative association in other studies³⁵.

Although none of the individual coexisting diseases was significantly associated with postoperative morbidity, the combined presence of several diseases in the old age patient group may be responsible for the observed significant association between age and morbidity.

A speculation about the underlying mechanisms of these observations should include the effects that both blood transfusions and impaired nutritional status have on the immune system^{33,34}. Apparently the effect of a large blood loss is more important than the effect of nutritional status. If this is an intrinsic effect of blood loss, or related with a possibly greater amount of blood transfusions in

these patients, is not subject of this study. But the use of blood transfusion is frequently associated with factors that may alter prognosis adversely³⁶. A deteriorated nutritional status seems to impair the ability of the host defense system to limit the progression of a complication.

5.6 Conclusion

The results of this study suggest that repletion by nutritional support diminishes the severity of complications, rather than preventing their development.

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The influence of perioperative nutritional intervention on postoperative complications

6.1 Abstract

Ever since methods of artificial nutritional support became available, attempts have been made using this form of treatment to reduce mortality and morbidity in surgical patients. Many trials have addressed this question, but very few have given a meaningful answer because of conceptual and methodological flaws. We therefore undertook a prospective randomised trial investigating the effects of at least 10 days preoperative total parenteral nutrition (TPN) (n=51) or total enteral nutrition (TEN) (n=50) providing 150% BEE non-protein energy, to reduce major postoperative complications or mortality in a homogeneous patient group with signs of depletion. Fifty patients served as a depleted control group (D) and 49 patients served as a non-depleted reference group and were operated upon without delay.

Depleted control patients suffered significantly more septic complications than patients in the non-depleted reference group did ($p<0.05$). There was no significant difference, however, in septic complications between either of the nutritional support groups and the non-depleted control group. In high risk patients, with weight loss $>10\%$ of body weight and over 500 ml blood loss during operation, a significant decrease ($p<0.05$) in major complications was observed as a result of nutritional support.

We conclude that preoperative nutritional support, in patients with severe depletion, results in a reduction of major complications to a degree that justifies its routine use in this selected group of patients.

6.2 Introduction

Many studies have demonstrated that parenteral nutrition can correct the effects of starvation¹⁻¹⁶. That depletion and loss of body cell mass induces loss of tissue function and are associated as single factors with a less favourable outcome of treatment of disease is well accepted. On the other hand, in surgical patients it is

often one of many factors determining surgical outcome. Whether correcting nutritional depletion under these circumstances influences outcome is less certain, although it has been the subject of several trials which have particularly addressed the effectiveness of preoperative parenteral nutrition in reducing postoperative morbidity and mortality. Unfortunately, most of these trials do not fulfill the minimum criteria with regard to design and number of randomised patients¹⁷. A recent large multi-centre trial¹⁸ of preoperative nutritional support suggested that the effectiveness of this treatment was confined to a limited group of patients with severe depletion. This study was designed to assess the clinical efficacy of preoperative nutrition in a relatively homogeneous group of patients studied in a single centre. The question of whether efficacy is confined to a subgroup of severely depleted patients was particularly addressed.

6.3 Patients and methods

6.3.1 Patients

Patients with newly detected, histologically proven gastric or colorectal carcinoma requiring surgical treatment, who had not undergone treatment for other malignant tumors were eligible to enter the trial.

As it was considered unethical to include patients over 80 years of age and patients with a normal nutritional status, patients in these categories were excluded from randomisation.

The study was reviewed and approved by the Human Studies Committee of the University Hospital Maastricht.

6.3.2 Nutritional assessment

The presence of depletion was determined in all patients using the following parameters: albumin (ALB), total lymphocyte counts (TLC) and percent ideal body weight (PIW), calculated from body length, body weight and wrist circumference using the Metropolitan Life tables¹⁹. These parameters were combined in a nutritional index ($NI = 0.14 \times ALB + 0.03 \times PIW + 0.73 \times TLC - 8.9$) that has been demonstrated in a previous study²⁰ to allocate correctly patients to groups that were on clinical grounds considered to be depleted or not. Values above the mean of the non-depleted group from that study (1.31) were considered to reflect a normal nutritional status.

6.3.3 Study design

After stratification for percent weight loss (PWL) ($<, \geq 15\%$), age ($<, \geq 65$ years) and tumor localisation (gastric/colorectal), patients were randomised to receive

preoperative parenteral nutrition (TPN) (group 1), preoperative enteral nutrition (TEN) (group 2) or to undergo surgery without delay (group 3). Non-depleted patients, with a nutritional index > 1.31 , served as a reference group and were monitored according to the trial guidelines (group 4). Patients in this group also underwent surgery without delay.

6.3.4 Nutritional support

Patients in group 1 were planned to receive 150% of basal energy expenditure (BEE), calculated using the Harris and Benedict equation²¹, as non-protein calories from a parenteral nutrition stock solution that contained 7 g N/l (Synthamin 14[®]) and 25% dextrose. Trace elements and vitamins (MVI[®]) were added conform today's standards. Electrolytes were added according to the individual patient's needs. Five hundred ml of an intravenous fat emulsion (Intralipid[®] 20%) was administered at least three times per week. Preoperative nutritional support lasted at least 10 days.

Patients in group 2 received enteral nutrition (Precitene[®] or Isotein[®]) either by nasogastric tube or by mouth. Caloric intake was planned to contain 150% of the calculated BEE during at least 10 days preoperatively.

Parenteral nutritional support was continued postoperatively in group 1 until the patients had resumed an oral diet providing 120% BEE. Postoperatively, patients in groups 2, 3 and 4 were allowed increasing amounts of liquids and solids as tolerated. Only in the event of a major postoperative complication, parenteral nutrition was started in these groups.

6.3.5. Morbidity and mortality

Complications, summarised in table 6.1, were monitored daily. The presence of each complication was evaluated separately. Finally, patients were categorised within each trial group as having suffered no complications, at least one minor complication (and no major complications) or at least one major complication. Mortality was evaluated separately.

6.3.6 Statistics

All patients in the trial groups were analysed according to the intention-to-treat principle. Data were summarised as means and standard deviations. Results were evaluated using Chi-square and Mantel Haenszel Chi Square tests for the complication frequency in the trial groups and an ANOVA procedure for comparison of the distribution of risk factors between trial groups. P-values smaller than 0.05 were considered to be significant.

Table 6.1: *Complication definition*

MINOR	
Wound infection	Clinical aspect, positive culture or necessity for surgical drainage
Urinary tract inf.	Positive culture >10 ⁷ micro-organisms/ml urine
Pulmonary tract inf.	positive sputum culture, abnormal chest X-ray requiring treatment with antibiotics
MAJOR	
Respiratory insuff.	Ventilatory assistance for > 12 hrs. postoperative or mechanical renewed ventilation after detubation.
Cardiac insuff.	Clinical and radiological diagnosis requiring cardiotonics and/or diuretics, or myocardial infarction confirmed on ECG or by serum enzyme elevations.
Renal insuff.	Plasma urea levels elevated by 50 % or a plasma creatinin elevation with 20%.
Intra-abd. abscess	Purulent fluid collection, demonstrated by ultrasound, or CT-scan guided drainage or at reoperation.
Fistula	Diagnosis on clinical grounds or proven by fistulography.
Anastomotic leakage	After clinical or radiological diagnosis, necessity for operation or drainage.
Wound dehiscence	Dehiscence of the wound requiring surgical closure.
Sepsis	Positive bloodculture, persisting temperature above 39° C., associated with hypotension and hypoperfusion.
D.I.C. syndrome	Positive FDP-test, abnormal clotting tests and decreasing thrombocyte counts.
Mortality	Any postoperative in-hospital mortality.

6.4 Results

6.4.1 Patients

Hundred-and-fifty-one patients entered the trial. Fifty-one patients were randomised to receive TPN and 50 patients to receive TEN, while 50 patients received no nutritional support and underwent surgery without delay. Forty nine patients served as a 'normal' reference group. The trial groups were comparable with respect to age, weight loss and the ratio gastric/colorectal cancer (Table 6.2).

The trial groups (1 – 3) and the reference group 4 were also comparable in terms of blood loss during operation and duration of the surgical procedure.

In group 1 more patients had advanced disease (stage IV cancer). The higher values of PIW, serum albumin and TLC and the lower PWL values in group 4 (reference group) were a consequence of the way this group was selected.

6.4.2 Nutritional support

In TPN patients (group 1) average preoperative energy intake ($\pm$ sd) was 1783 ($\pm$ 350) kcal per day with 11.9 ($\pm$ 2.5) gram nitrogen per day and 9.4 ($\pm$ 5.7) % fat; the N/kcal ratio was 1:168 ($\pm$ 20). The average ($\pm$ sd) preoperative caloric intake in TEN patients (group 2) was 1458 ($\pm$ 444) kcal per day with 20.5 ($\pm$ 5.5) gram nitrogen per day, 27.4 ($\pm$ 8.3) % of total energy intake as fat and a

Table 6.2: Study population

	T.P.N.	T.E.N.	Depleted	Non depleted
n	51	50	50	49
age (mean + std)	67 (10)	66 (9)	66 (7)	61 (10)
age (range)	41-80	39-78	49-79	39-77
G/CR cancer	15/36	13/37	14/36	10/39
M/F ratio	29/22	32/18	32/18	33/16
STAGE n (%)				
I	13 (26%)	12 (24%)	15 (30%)	24 (48%)
II	5 (10%)	7 (14%)	3 (6%)	3 (6%)
III	15 (30%)	20 (40%)	19 (38%)	14 (29%)
IV	18 (36%)	11 (22%)	13 (26%)	8 (17%)
	mean (std)	mean (std)	mean (std)	mean (std)
P.I.W. (%)	95 (12)	98 (12)	98 (11)	113 (12)
P.W.L. (%)	8 (6)	6 (7)	6 (6)	4 (6)
Albumin (g/l)	34 (4)	36 (4)	34 (4)	39 (3)
T.L.C. (/mm ³)	1.7 (0.5)	1.7 (0.5)	1.8 (0.6)	2.5 (0.7)
Blood loss (ml)	770 (760)	820 (1030)	830 (1030)	990 (1350)
Duration of procedure (hr.min)	2.50 (1.2)	2.50 (1.1)	3.00 (1.0)	3.30 (1.4)

N/kcal ratio of 1:102 (± 26). The ranges of the nutritional support data are summarised in table 3: the lower values indicating the values at the start of nutritional support, the higher ones indicating the level reached after the initial 2 days (Table 6.3).

6.4.3 Complications

6.4.3.1 Technical complications

Complications resulting from the nutritional intervention itself include: in the TPN group: 1 arterial puncture and 1 pneumothorax requiring drainage

Table 6.3: Nutritional support

	T.P.N.	T.E.N.
preoperative support days	11.8 (10 - 23)	11.4 (10 - 15)
kcal/N	157 - 173	102 - 109
% fat	5 - 12	26 - 27
carbohydrates (kcal/day)	1375 - 1885	1345 - 1575
fat (kcal/day)	85 - 250	535 - 555
N (g/kg BW/day)	0.16 - 0.20	0.31 - 0.34
Prot (g/kg BW/day)	0.97 - 1.25	1.90 - 2.09

as a result of the catheter insertion procedure; and 4 clinically or bacteriologically proven episodes of catheter sepsis, requiring removal of the catheter. Complications in the TEN group included diarrhoea requiring treatment in 3 patients, vomiting in a further 3 patients, and a delayed gastric emptying in 2 patients, resulting in gastric retention of the administered food. No episodes of ileus, or aspiration were observed.

Table 6.4: Postoperative complications

complications	T.P.N.	T.E.N.	Depleted	Non-depleted
n	51	50	50	49
Woundinfection	8	7	8	13
Urinary tract infection	16	10	10	9
Resp. tract infection	14	8	7	6
Wound dehiscence	2	1	2	1
Anastomotic leakage	5	4	7	3
Fistula	2	2	1	0
Intra abd. abscess	4	4	8*	0*
Sepsis	1	1	4*	0*
Resp. insuff.	0	2	2	2
Circ. insuff.	1	1	0	0
Renal insuff.	0	0	0	0
Mortality	2	4	2	1
sepsis related mortality	1	2	2	0
* $p < 0.05$ χ^2 -test				

6.4.3.2 Postsurgical complications

The number of complications per study group is summarised in table 6.4. No significant differences were present between study groups for most complications. Complications categorised as minor or major are summarised in table 6.5 while mortality is shown separately. If summarised in this way no significant differences were observed between the groups (Table 6.5). The number of complications occurring in each patient is summarised in table 6. There were fewer patients with more than 1 complication in the non-depleted, T.P.N. and T.E.N. groups than in the depleted group. If the number of complications is given a separate weight (e.g. 1 complication eq 1, 2 complications eq 2, 3 complications eq 3) the distribution of number of complications is significantly different between groups: TPN and TEN seem to reduce the number of complications per patient, compared to the depleted control group 3.

Table 6.5: Postoperative complication groups

	T.P.N.		T.E.N.		Depleted		Non-depleted	
complications	n	%	n	%	n	%	n	%
no	24	47.1	26	52.0	32	64.0	28	57.2
minor	19	37.2	14	28.0	9	18.0	17	34.7
major	6	11.8	6	12.0	7	14.0	3	6.1
mortality	2	3.9	4	8.0	2	4.0	1	2.0
Chi-square and Mantel-Haenszel				p (χ^2)	p (MH)			
Total group				0.45	0.16			
Group TPN vs TEN vs Depleted				0.24	0.29			
Group TPN vs Depleted				0.19	0.39			
Group TEN vs Depleted				0.48	0.33			
Group TPN and TEN and Depleted				0.40	0.26			
vs Non-depleted								
Group Depleted vs Non-depleted				0.20	0.76			

p-Values of χ^2 -test and Mantel-Haenszel for combinations of intervention groups versus depleted patients of reference groups. In non of the combinations a significant difference is observed.

Table 6.6: Number of multiple major septic postoperative complications

	T.P.N.	T.E.N.	Depleted	Non-depleted
no/minor complications	43	40	41	45
pat. with 1 complication	1	3	0	1
pat with 2 complications	3	3	5	2
patient with 3 complications	1	0	3	0

Significant reduction (χ^2 : $p < 0.05$) of major septic complications in supported groups.

The stratification for weight loss allowed for performance of a subset analysis in the patient group displaying more severe depletion. This analysis showed a significant decrease in the number of patients developing an intraabdominal abscess in the TPN and TEN groups to become significant (Table 6.7). The differences between the intervention groups and the depleted control group became more pronounced in the subset of patients suffering major peroperative

blood loss (Table 6.8). The patient characteristics as described in table 2 were not different between groups in either of these subset analyses.

Table 6.7: Postoperative complications in patients with PWL > 10%.

	T.P.N.	T.E.N.	Depleted	Non-depleted
n	18	13	11	8
Anastomotic leakage	1	2	3	2
Intra-abd. abscess	0* ⁺	2* ⁺	4* ⁺	2*
Sepsis	0	1	2	0
* p < 0.05 TPN vs TEN vs Depleted vs Non-depleted				
+ p < 0.05 TPN and TEN vs Depleted				

Table 6.8: Postoperative complications in patients with peroperative blood loss > 500 ml.

	T.P.N.	T.E.N.	Depleted	Non-depleted
n	25	21	20	23
Anastomotic laekage	3	3	6	3
Intra-abd. Abscess	2* ⁺	3* ⁺	7* ⁺ #	2* [#]
Sepsis	1* ⁺	1* ⁺	4* ⁺ #	0* [#]
* p < 0.05 TPN vs TEN vs Depleted vs Non-depleted				
+ p < 0.05 TPN and TEN vs Depleted				
# p < 0.05 Depleted vs Non-depleted				

6.4.4 Hospital stay

Total hospital stay of the reference group 4 was significantly shorter than that of the other groups. Total hospital stay in the TPN group was 36.3 ($\pm$ 17.7) days, in the TEN group 33.3 ($\pm$ 20.2) days, in depleted control group 31.7 ($\pm$ 22.1) days. This difference was not significant. In the reference group this was 24.8 ($\pm$ 11.3) days and differed significantly from the trial groups (ANOVA p<0.01). Hospital stay in both the TPN and TEN group was no longer than that of the untreated group 3, even though a longer preoperative hospital stay was present in the nutritional support groups (11.5 days in group 1 and 9.9 days in group 2, compared to 5.0 days in the depleted control patients. This would suggest a shorter postoperative hospital stay in the TPN and TEN groups. Due to a large variation in these data the difference did not become statistically significant. As

was to be expected, postoperative hospital stay increased significantly in patients with minor or major complications ($p < 0.001$). Analysis of the patients with complications as a group did not reveal a beneficial effect of perioperative nutrition on total hospital stay. Postoperative hospital stay was shorter, albeit not significantly, for both TPN and TEN groups if patients had suffered a major complication.

6.5 Discussion

Cancer patients frequently show signs of depletion as a result of an often prolonged disturbance of energy balance. Although increased energy expenditure has long been thought a major contribution to the disturbance of energy balance, most physicians now agree that decreased energy intake, in most cases, is the more important determinant of the development of cancer associated depletion.

Parameters describing depletion have been identified as surgical risk factors. Thus weight loss and ideal weight, plasma proteins and various derived nutritional indices have all shown a significant association with operative outcome^{6,7,11,22-35}. The availability of various forms of artificial nutrition has resulted in efforts to demonstrate a clinical benefit of perioperative nutritional support^{2,4,6-11,13,36-40}. Most trials suffer from major conceptual flaws¹⁷ and have included non depleted patients. Our trial has overcome most of these problems by testing the effects of 10 days of perioperative nutritional support in depleted patients only, in a prospective randomised design against immediate operation, without nutritional support. The results of our trial suggest a small benefit with fewer episodes of sepsis and less intra-abdominal abscess formation. This effect was more pronounced in the more severely depleted patients and was not obtained at the cost of increased morbidity of the nutritional support technique itself.

Depletion was defined in this study by means of a 'nutritional index'^{1,20}. This index is derived from serum albumin, total lymphocyte count and percent ideal weight, which reflect the disease process as well as nutritional depletion. Plasma albumin concentrations remain normal even during prolonged periods of simple starvation⁴¹, but decrease rapidly in the presence of disease, due to changes in distribution. Although little is known concerning the total lymphocyte count in starvation, TLC values decrease rapidly in septic conditions. Any anthropometric parameter is influenced by fluctuations in fluid retention. As none of these patients suffered from severe metabolic stress or fluid retentions, low PIW values may reflect nutritional depletion as well as the presence of cancer.

The results of the current trial are in line with the two most important trials performed in this field^{6,18}. The data from the trial reported by Mueller et al.⁶ have never been considered convincing enough to cause preoperative nutrition to become common practice. Patients in that trial were not stratified for depletion and the control group stayed in hospital for preoperative work-up for almost as long a period as the nutritional intervention group. The results of that trial may be interpreted as suggesting that prolonged starvation results in a worse outcome than if nutritional support is administered. Our observation that nutritional support reduced infectious complications in severely depleted patients, confirms the observation in the Veterans Administration trial¹⁸ that was not statistically significant possibly because of the number of patients showing severe depletion was too small. That our results are significant in contrast to those of the VA-trial¹⁸ may be explained by the fact that we investigated a more homogeneous patient group, operated in only one hospital, by a limited number of surgeons, with a reasonable result (5% mortality vs 10% in the VA-trial).

The ability to respond to intrusions is only in part dependent on 'nutritional status'. Other factors such as cardio-respiratory status are far more crucial in many cases. Nutritional support, therefore, is only one factor affecting outcome and is of varying importance in different patients. Nutritional depletion increases the risk of perioperative complications, but not to the extent that all depleted patients develop complications. It is, therefore, unreasonable to expect complete eradication of all postoperative complications by nutritional support.

6.6 Conclusion

From the results of this trial we therefore advocate that only patients with signs of (severe) depletion (i.e. weight loss >10%) receive nutritional support prior to surgery. The benefit of such treatment increases with the degree of the initial depletion. These observations may possibly be extended to other conditions where patients are planned to undergo chemotherapy, radiotherapy and surgery.

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The relation of preoperative surgical risk parameters with long term survival of patients with gastric and colorectal cancer

7.1 Abstract

Indicators of depletion and surgical risk have prognostic significance with regard to the response to medical or surgical therapy. Several studies suggested after monofactorial analyses a significant association of depletion and other surgical risk indicators with long term survival. It has been questioned, however, whether these significant associations are independent associations. We therefore analysed in a prospective study the effect of parameters commonly used to assess preoperative depletion on long term survival in 201 consecutive patients admitted for surgical treatment of gastric or colorectal cancer. Stage of disease, preoperative percent weight loss, percent ideal body weight, plasma protein, plasma albumin, plasma pre-albumin concentration and blood loss were significantly correlated with long term survival (Kaplan-Meier, log rank $p < 0.05$) in both gastric and colorectal cancer.

A Cox regression analysis yielded independent effects for depletion related parameters (ideal weight, albumin, hemoglobine) and blood loss. We conclude that depletion has an adverse effect on long term survival of patients with gastric or colorectal carcinoma, that is independent from the stage of disease.

7.2 Introduction

Parameters that indicate depletion are of prognostic significance with regard to the response to medical therapy and risk for postoperative complications. Already in 1936 a markedly increased mortality rate was observed after surgical treatment of chronic peptic ulcer patients who had suffered a more than 20 per cent weight loss¹. Furthermore, weight loss and decreased levels of albumin have been associated with increased postoperative morbidity and mortality^{2,3} (Chapter 3).

Few studies have addressed the prognostic significance of depletion indicators on long term survival. DeWys et al.⁴ found a significantly decreased median survival of colorectal cancer and gastric cancer patients who had experienced more than 10% weight loss compared to weight stable patients. Lanzotti⁵ found weight loss to be the most important prognostic indicator of survival in patients with inoperable lung cancer. Wiggers⁶ demonstrated significantly decreased survival after surgical treatment of colorectal cancer in patients with serum total protein values under 65 gr/l. Phillips⁷ showed low 'pre-disease' albumin values to be associated with increased mortality rates of cardiovascular disease and cancer in a large population.

It has been questioned, however, whether the effect of depletion on long term survival is an independent effect. The aim of the current study was to analyse prospectively the associations of depletion, stage of disease, and surgical procedure related factors with long term survival after surgical treatment of gastric or colorectal cancer.

7.3 Patients and methods

7.3.1 Patients

Two hundred and one consecutive patients (126 males, 75 females) admitted to undergo surgery for newly detected and pathologically confirmed gastric (n=52) or colorectal (n=149) cancer entered this study. Patients aged over 80 years were excluded.

The study was reviewed and approved by the Human Studies Committee of the University Hospital Maastricht and informed consent was obtained from each subject. The study was started in oktober 1983 and lasted until januari 1988.

7.3.2 Study design

On admission blood was drawn from all patients to determine hemoglobin, white blood cell count, total lymphocyte count, total protein, albumin, pre-albumin, transferrin, electrolyte status, creatinin, urea. Preoperative anthropometric evaluation included determination of weight, weight loss during the previous year, and height. Percent ideal body weight⁸ (PIW) and percent weight loss were calculated. Peroperative blood loss was estimated and postoperative complications were scored until hospital discharge. Postoperative complications were categorised as absent, minor (including woundinfection, urinary or pulmonary tract infections) or major complications (including respiratory, renal, hepatic or cardiac failure, intra-abdominal abscess or fistula formation, anastomotic leakage, wounddehiscence, sepsis, diffuse-intravascular-coagula-

tion-syndrome and mortality).

Part of the patients had participated in a prospective randomised trial investigating the efficacy of perioperative nutritional support to reduce postoperative complications in depleted patients. Therefore, the administration of nutritional support was taken into account. The results of perioperative nutritional support on long term survival are reported in chapter 8.

Records of all patients were reviewed to assess survival and cause of death in may 1991, after a follow-up period of at least 42 months. Survival was recorded from the time of surgery until death from any cause.

7.3.3 Statistical analysis

Parameters among groups were tested by ANOVA, complication ratios were analysed using Chi-Square analysis. Life table (actuarial) survival analyses for all patients as well as for subgroups were performed using the Kaplan-Meier method⁹. The survival curves of groups of patients were compared using the log-rank test¹⁰.

The combined and independent effects of the predictor variables on survival were analysed using a Cox (proportional hazards) non-parametric multiple regression model¹¹ for censored survival data (BMDP2L). This model allows simultaneous estimation of the relative effect on survival of each variable, adjusted for the effects of correlations with the other prognostic variables included in the model. This regression model included all preoperative parameters which appeared to be important in the log-rank analysis ($p < 0.05$), and the depletion parameters. Factors not showing significant independent association with long term survival were removed step by step, provided the removal of a factor did not cause a large shift in the coefficients of the remaining factors. Perioperative nutritional support parameters were always kept in the model to exclude confounding effects. P-values smaller than 0.05 were considered significant.

7.4 Results

7.4.1 Patients

Hundred-and-fifty patients were randomised into three groups. Fifty patients received on average 21 days of perioperative parenteral nutritional support, and 50 patients received 10 days of preoperative enteral nutrition (Chapter 6 & 8). Preoperative parameters of both groups are listed in table 7.1. The administration of perioperative nutritional support did not affect the complication rate in overall patients groups (chi-square ns, Chapter 6).

All deaths were G.I. cancer related, except for 3 patients; one died in a traffic accident, one of a primary lung carcinoma, and one patient committed suicide.

Table 7.1: Preoperative characteristics

	Gastric cancer n=52		Colorectal cancer n=149	
	mean	std	mean	std
Total protein (g/l)	70	8	71	7
Albumin (g/l)	35	4	36	5
Pre-albumin (g/l)	0.25	0.08	0.24	0.07
Hemoglobin (mmol/l)	8.0	1.6	8.0	1.5
Lymphocyte count (/mm ³)	1.90	0.83	1.92	0.62
Age	64	11	65	9
P.I.W.	97	14	101	15
P.W.L.	11	16	6	8
Duration of procedure (hr.min)	3.20	1.33	2.55	1.15
Peroperative blood loss (ml)	910	980	820	1080

7.4.2 Survival

Overall 5-year survival in the current study was 45% in the colorectal cancer patients and 40% in the gastric cancer group. This difference was not significant.

Figure 7.1 shows the overall survival curves for patients with gastric and colorectal cancer. Figure 7.2 shows the survival curves for patients with different tumor stages in gastric and colorectal cancer patients. We found a 80% 5-year survival of gastric cancer and 70% 5-year survival in colorectal cancer in stage I and II, a 45% 5-year survival in stage III both gastric and colorectal cancer and no 5-year survival in stage IV gastric and colorectal cancer.

Figure 7.1: Overall survival for gastric and colorectal cancer patients as estimated with the Kaplan-Meier method. (log rank ns)

The results of comparisons of the survival curves for several individual parameters with given cut-off points are summarised in table 7.2. Significant differences in survival curves for groups of patients defined by tumorstage (stage I to IV), albumin ($<$, $\geq$ 35 gr/l), total protein ($<$, $\geq$ 60 gr/l), pre-albumin ($<$, $\geq$ 0.20 g/l), weight loss ($<$, $\geq$ 10%), percent ideal weight ($\leq$, $>$ 95%), and blood loss ($<$ 500, 500-1000, 1000-1500, $>$ 1500) were observed.

Figure 7.2: Overall survival for separate stages of gastric (top) and colorectal cancer (bottom) as estimated with the Kaplan-Meier method. Stage III (log rank $p < 0.01$) and stage IV (log rank $p < 0.0001$) differ significantly from stage I and II.

Figure 7.3 shows the influence of PIW above and below 95% on survival in GI cancer patients. Median survival is 48 months in gastric cancer patients and 76 months in colorectal cancer patients with a PIW above 95%. Median survival is 13 months in gastric cancer patients and 42 months in colorectal cancer patients in the group below 95% of ideal weight.

Figure 7.4 shows the influence of albumin above and below 35 g/l on survival in GI cancer patients. Median survival was over 90 months in patients with an albumin above 35 g/l both in gastric and colorectal cancer and 20 months in gastric cancer patients and 36 months in the colorectal cancer patients in the group below 35 g/l.

Figure 7.5 shows the influence of blood loss in GI cancer patients. The patients with higher amounts blood loss showed decreasing survival rates.

Figure 7.3: The association of ideal body weight ($\leq, > 95\%$) with survival of gastric (top) and colorectal cancer patients (bottom) in all stages of disease. (log rank $p < 0.05$, resp Wilcoxon $p < 0.05$)

Figure 7.4: The association of albumin above and below 35 g/l with survival of gastric (top) and colorectal cancer patients (bottom) in all stages of disease. (log rank $p < 0.01$, resp. $p < 0.025$)

Figure 7.5: The association of peroperative blood loss (<500, 500-1000, 1000-1500, >1500ml) with the survival of gastric (top) and colorectal cancer patients (bottom) in all stages of disease. (log rank ns, resp. $p<0.01$)

Table 7.2: Results of log-rank tests for comparison of survival curves.

	Group definition cut-off points	Log rank test p-value	
		gastric	colorectal
Tumor stage	stage I-IV	0.0001	0.0001
Albumin	35 g/l	0.01	0.05
Total protein	60 g/l	0.05	0.05
Pre-albumin	0.20	0.05	0.001
P.W.L.	10%	0.05	0.0005
P.I.W.	95%	0.05	0.05
Hemoglobin	6 mmol/l	ns	0.01
Lymphocyte count		ns	ns
Peroperative blood loss	<500, 500-1000, 1000-1500, >1500 ml	ns	0.01
Duration of operation		ns	ns
Postoperative complications	no. minor, major	0.01	0.01
Nutritional support	no. TPN, TEN	ns	ns
Age		ns	ns
Sexe	Male, Female	ns	ns

For each significant different parameter the group defining cut-off points are given.

7.4.3 Cox-regression

The parameters yielding a significant result in the log-rank test summarised in table 7.2, as well as the indicators of nutritional support, tumor localisation and depletion parameters, were subsequently considered as explanatory variables in a Cox-regression model. Stepwise reduction of factors, deleting the least significant factor, resulted in a list of factors with a significant association with survival. Table 7.3 shows the result of this analysis. As expected, the most important factor was tumorstage. Comparison of stage II, III and IV with stage I showed an increasing risk of dying in higher stages. Stage II was not associated with a significantly increased risk of dying compared to stage I, whereas stage III and stage IV were. The analysis furthermore showed that at any point in time the risk of dying in stage IV was about 53 times ($\exp(\text{coeff})$) that of stage I. The occurrence of postoperative complications did not show significant effects on long term survival. Furthermore, PIW and albumin were significantly associated with long term survival. The proportional risk of dying is reduced by two-thirds in patients with a PIW above 95% compared with patients with a PIW below

95%. The proportional risk of dying is reduced with 0.92 with every increasing unit of albumin: a patient with a plasma albumin concentration of 40 g/l has a reduced hazard of dying amounting to $(0.92)^5 = 0.66$ compared to a patient with an albumin value of 35 g/l.

The administration of perioperative nutrition was included in the model as a possible confounder. There was no improvement of long term survival by routine perioperative feeding on long term survival in the total population, nor was there an adverse effect on long term survival by perioperative nutrition.

Preoperative hemoglobin levels were also significantly associated with long term survival (Figure 7.6).

Table 7.3: Stepwise multivariate analysis

	Coeff/se	Exp(coeff)	p
Stage II	-	-	ns
Stage III	2.1788	2.9793	0.025
Stage IV	7.0863	52.8511	0.0001
Preop. nutrit. support	-	-	ns
TPN/TEN	-	-	ns
Tumor localisation	-	-	ns
Hemoglobin	2.6030	1.2789	0.01
Albumin	-2.2666	0.9218	0.025
PIW (<,> 95%)	-1.7154	0.6383	0.05
Blood loss	2.4175	1.3030	0.01

The table lists in the first column estimated coefficient/standard error (coeff/se) or the z -statistics. The second column of data lists the relative risk estimate (equal to $\exp(\text{coeff})$), while the last column of the table lists the p -value of the likelihood ratio test for significance of the factor (after correction for the other factors).

Figure 7.6: The association of preoperative hemoglobin levels ($<$, $\geq 6 \text{ mmol/l}$) with the survival of gastric (top) and colorectal cancer patients (bottom) in all stages of disease. (log rank ns, resp. log rank $p < 0.01$)

However, not a low hemoglobin, but the presence of high hemoglobin levels was independently associated with a decreased survival in the Cox-regression analysis (Table 7.3). Further analysis of this unexpected effect showed a strong correlation of preoperative hemoglobin levels and albumin levels with tumor stage, specifically with stage IV. It appears that the high coefficient for the stage IV variable 'overshoots' the risk ratio for low albumin, high hemoglobin patients. The presence of low albumin (<35 g/l) and low hemoglobin (<6 mmol/l) was observed in 17 patients, with 12 patients in stage IV (Figure 7.7). The high additional negative influence of stage IV in this subgroup of patients (Hb <6 , Alb <35) pulls the coefficient of hemoglobin to a positive value. The lower rectangle in each quadrant shows the relative risk (logRR) of hemoglobin and albumin in each subgroup, the upper polygonal the contribution of the relative risk (logRR) of stage I, II, III and IV, with the widths of the bars relative to the numbers of patients in each stage. The total area represents the mean log RR for the quadrant. The coefficient, after taking into account the stage of disease, shows then the highest hazard of dying was observed in the group with preoperative hemoglobin levels < 6 mmol/l and albumin levels < 35 g/l, mainly due to the large contribution of stage IV patients. This is shown also in figure 7.8 where hemoglobin levels, plasma albumin values and survival are plotted for each separate stage. Low hemoglobin levels and low albumin values have shorter survival than high hemoglobin levels and albumin values, but nearly all patients are in stage IV of disease. The same is illustrated in figure 7.9 where a three dimensional regression surface is drawn for the data shown in figure 7.8. Low hemoglobin and low albumin values show the shortest survival.

Figure 7.7: The relative contributions to the log RR (relative risk) in each quadrant of hemoglobin levels, plasma albumin values and stage (see text for explanation).

Figure 7.8: 3D scatter plot of survival for stage, plasma albumin values and hemoglobin levels. Clearly is shown that low plasma albumin values, low hemoglobin levels, and especially the combination of both have the shortest survival as can be expected from clinical experience.

Figure 7.9: The same data analysis of figure 7.8 is shown in this third order regression surface drawn through the points of figure 7.8.

7.5 Discussion

This study was performed to assess whether the association between depletion and decreased survival of gastric or colorectal cancer patients, as has been described previously by several authors¹, is independent from tumor stage.

This study confirms that the stage to which a malignancy of the GI tract has progressed is the most important determinant of survival. We found a 54% 5-year survival in colorectal cancer and 40% in gastric cancer, which is consistent with the literature¹²⁻¹⁴. In the current study 80%, respectively 70% 5-year survival of gastric and colorectal cancer patients in stage I and II, 45% 5-year survival of patients in stage III and no 5-year survival in stage IV was observed. Again this is consistent with literature¹⁵. Our observation that stage II disease was not associated with a significantly increased risk of dying is presumably related to the relatively short mean follow up period of 45 months. A longer follow-up period may show a difference.

Percent ideal body weight was a significant independent riskfactor in the total study population. This is consistent with the literature where in mono factorial analyses percentage weight loss and ideal body weight have been described to have prognostic value with respect to a patient's postoperative morbidity and mortality¹⁶⁻¹⁹, and long term survival^{4,5,7,20}. Weight loss is not a significant predictor in the Cox regression analysis because of the high correlation with ideal body weight. Weight loss is a common feature of cancer, negatively influencing treatment results and survival. Weight loss, and eventually cachexia, may be caused by several mechanisms²²⁻²⁵. Although it has long been thought that the association of weight loss and low plasma albumin levels with long term survival reflects progressing tumor stages, we now demonstrate this phenomenon to be independent from tumor stage. It is possible that weight loss and cachexia are epiphenomena of the metabolic relation between host and tumor.

In addition, low plasma albumin values showed in the current study a significant independent association with decreased survival. Most likely hypoalbuminaemia does not reflect depletion, but rather the metabolic response elicited by the presence of a tumor, in which plasma albumin behaves as a negative (acute) phase protein²¹.

In the Cox-regression analysis blood loss was significantly correlated with long term survival of these patients. Blood transfusion²⁶⁻²⁹ has been claimed to correlate significantly with long term survival. An association between peri-operative blood transfusions and decreased long term survival of colorectal cancer patients^{26,27,29,30} as well as breast cancer patients²⁸, has been reported for some time, other studies failed to prove a relationship between transfusion and survival or recurrence rate of colonic cancer³¹⁻³³ or breast cancer³⁶ patients.

Together with the reported prolonged graft survival after concomitant blood transfusion in renal transplantation procedures³⁴ these findings suggest an immunosuppressive effect of transfusion. Allogeneic blood induces a wide scale of antigen specific and non-specific effects on T lymphocytes and phagocytic cell function³⁵⁻⁴⁰. The significant association of peroperative blood loss and preoperative hemoglobin concentrations in our study correspond well with this finding. It is attractive to hypothesise that the same phenomenon could be responsible for this finding. Otherwise peroperative blood loss could indicate more extensive surgical procedures at difficult attainable sites in more advanced stages of cancer. But the significant effect of blood loss remained present even after correction for some of these factors in the multivariate analysis.

7.6 Conclusion

Stage of disease is the most important predictor of long term survival of GI cancer patients. In our study, blood loss and depletion parameters have also independent effects on long term survival of GI cancer patients. No adverse effects of perioperative nutrition on long term survival were seen.

The impaired nutritional status possibly reflects a quality of the impact the tumor has on the host, resulting in decreased long term survival. In the future it is of interest to investigate whether manipulation of this metabolic relationship, e.g. by nutritional intervention, results in improved long term survival. Further trials investigating the impact of nutritional intervention on long term survival are therefore warranted.

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Influence of perioperative nutritional intervention on long term survival of patients with advanced colorectal cancer

8.1 Abstract

Indicators of depletion have prognostic value with regard to the incidence of postoperative complications and to long term survival. The effects of perioperative nutrition on tumor growth and long term survival of GI tract cancer patients have not been documented.

In this prospective randomised controlled study the effect of perioperative nutritional intervention on long term survival is investigated in 149 consecutive patients (62 females, 87 males) admitted for surgical treatment of newly detected colorectal cancer. Depleted patients in stage IV colorectal cancer survived significantly shorter than non-depleted patients. Depleted stage IV colorectal cancer patients receiving perioperative nutritional support survived significantly longer than depleted patients who received no nutritional support (log rank $p < 0.05$). No differences were observed in stage I, II and III. No differences among groups were observed with regard to tumorlocalisation, tumorload, age, sex and preoperative depletion indicators.

We therefore conclude that perioperative nutritional support has a beneficial effect on survival of stage IV colorectal cancer patients showing signs of depletion.

8.2 Introduction

Nutritional status parameters have prognostic value with regard to the incidence of postoperative complications and to long term survival¹⁻⁵. Perioperative nutritional support in depleted cancer patients has resulted in improved postoperative recovery⁶⁻⁸. However, a potential hazard of nutritional support of a cancer patient is enhanced tumor growth. Increased tumor growth and fat storage have been demonstrated in parenterally fed tumor bearing rats⁹. The response to nutritional support seems to be dependent on tumor load: repletion of serum protein levels and body weight, and reversed anergy have been

reported to occur in tumor bearing rats with a tumor load of less than 5%, while a tumor load of more than 25 % inhibited repletion of these parameters^{10,11}.

No data are available concerning the effect of perioperative nutrition on long term survival of depleted cancer patients. We therefore performed a prospective study to investigate these effects on long term survival of colorectal cancer patients.

8.3 Patients and methods

8.3.1 Patients

The effect of perioperative nutritional support was prospectively studied in 149 consecutive patients (62 females, 87 males) admitted to undergo surgery for newly detected colorectal cancer between oktober 1983 until january 1988. Patients aged over 80 years were excluded.

8.3.2 Study design

Because it was considered ethically unjustified to subject patients having a normal percentage ideal body weight (PIW), plasma albumin (Alb) and total lymphocyte count (TLC) to nutritional intervention, these patients were excluded from randomisation. In 1985 we computed an index¹² consisting of these parameters which could distinguish patients that were on clinical grounds judged to be nutritionally depleted, from a healthy control group by using the next formula:

$$(0.14 \times \text{Alb (g/l)}) + (0.03 \times \text{PIW (\%)}) + (0.73 \times \text{TLC (10}^9\text{/mm}^3\text{)}) - 8.90$$

In the current study all cancer patients who had an index below the mean of the healthy reference group (1.31) were randomised. Thirty-nine (26 males, 13 females) had an index value above 1.31 and were therefore excluded from randomisation. They served as non-depleted control group (ND). Of the remaining 110 patients (49 males, 61 females) with a value below the cut-off point, 36 were randomised to receive T.P.N., 37 enteral nutrition (T.E.N.), while 37 served as depleted controls (D).

8.3.3 Data collection

Blood was sampled preoperatively from all patients to determine hemoglobin, WBC, TLC, total protein, albumin, and pre-albumin. Preoperative anthropometric evaluation included determination of weight, height, weight loss during the preceeding year, and percent weight loss (PWL). PIW was calculated

using the Metropolitan Life tables¹³.

Peroperative blood loss was estimated. Postoperative complications, scored until hospital discharge, were categorised as absent, minor (including wound-infection, urinary or pulmonary tract infections) or major (including respiratory, renal, hepatic or cardiac failure, intra-abdominal abscess or fistula formation, anastomotic leakage, wounddehiscence, sepsis, diffuse intravascular coagulation-syndrome, and mortality).

Records of all patients were reviewed to assess survival and cause of death in may 1991, after follow-up period of at least 42 months. All deaths were cancer related, except for 3 patients; one died in a traffic accident (stage III, enteral group), one of a primary lung carcinoma (stage III, depleted control group), and one patient committed suicide (stage I, non-depleted group).

8.3.4 Nutritional support

As preoperative nutritional support patients received at least 150% of their basal energy expenditure (BEE) as calories, calculated with the Harris-Benedict formula¹⁴, during at least 10 days. Patients in both control groups were operated without delay. Postoperative parenteral nutrition was continued in the T.P.N. group until patients were able to take 120 % BEE orally.

T.P.N. solutions were prepared in the hospital pharmacy according to current standards. Basis solutions contained 7 gr N per liter (Synthamin 14[®]), 25 % glucose per liter. Intravenous lipid emulsions were administered at least 3 times weekly (500 ml Intralipid[®] 20 %). Vitamins (MVI[®]) and trace metals (zinc, copper, manganese, selenium, chromium, and iodine) were supplemented daily. Electrolytes (potassium, sodium, magnesium, calcium, chloride, phosphate) were supplemented according to the individual patient's needs.

Enteral nutrition, (Precitene N or Isotein[®] (N:kcal ratio 1:92, protein 107 gr/l, 1575 kcal/l)), was administered by naso-gastric tube or orally.

8.3.5 Statistical analysis

All patients were analysed according to the intention-to-treat principle. Parameters among groups were tested by ANOVA, complication ratios were analysed using Chi-Square analysis. Survival was analysed using the Kaplan-Meier method¹⁵. The survival curves of groups of patients were compared using the log-rank test¹⁶. The combined and independent effects of the predictor variables on survival were analysed using a Cox (proportional hazards) non-parametric multiple regression model¹⁷ for censored survival data (BMDP2L). This model allows simultaneous estimation of the relative effect on survival of each variable, adjusted for the effects of correlations with the other prognostic variables included in the model. This regression model included all preoperative

parameters which appeared to be important in the log-rank analysis ($p < 0.05$), the nutritional status parameters, and depletion parameters. P-values smaller than 0.05 were considered significant.

8.4 Results

8.4.1 Nutritional support

Six patients in the T.P.N. group refused participation in the trial (non in stage IV). In one patient (stage IV) the catheter was removed on the second day after signs of catheter sepsis. The other patients in the T.P.N. group received an average of 12.3 days (range 10 - 18 days) of preoperative parenteral nutritional support. On average patients in the T.P.N. group received 11.2 days (range 7 - 36 days) of postoperative parenteral nutritional support.

Six patients in the T.E.N. group refused participation in the trial (one stage IV), one patient was unable to receive enteral nutrition because of bowel obstruction. The other patients in the T.E.N. group received 10.5 days (range 9 - 14 days) of preoperative enteral nutritional support. After operation, the patients in the T.E.N. group received regular i.v. fluids until oral intake could be resumed.

Three patients in the T.E.N.-group (one stage IV) and 6 patients in the depleted control group (one stage IV) received T.P.N. after operation because of their inability to resume oral nutrition (table 8.1).

Table 8.1: Perioperative nutritional support

	TPN n=36		TEN n=37		Depleted n=37		Non depleted n=39
	mean	range	mean	range	mean	range	
Preop. support days	12.3	9-18	10.5	9-14	-	-	-
patients with postop. TPN	n=35		n=3		n=6	-	
Postop. TPN days	11.2	7-36	34.3	26-42	25.8	10-66	-
Stage IV patients	n=11		n=7		n=8		n=6
postop. TPN	n=10		n=1		n=1	-	
postop. TPN days	11.6	8-17	42	42	66	66	-

Duration of pre- and postoperative nutritional support and the number of patients with parenteral nutrition. Patients in the enteral, depleted and non-depleted group resumed oral regimen according to normal postoperative standards.

No difference in preoperative biochemistry and anthropometric data was observed between the trial groups (table 8.2). The non-depleted reference group had significant better preoperative parameters.

Table 8.2: Pre- and peroperative parameters

	TPN n=36		TEN n=37		Depleted n=37		Non depleted n=39	
	mean	range	mean	range	mean	range	mean	range
Total protein (g/l)	69	5	70	8	69	6	75*	6
Albumin (g/l)	34	4	35	4	34	4	39*	3
Pre-albumin (g/l)	0.22	0.08	0.23	0.06	0.22	0.08	0.30	0.05
Hemoglobin (mmol/l)	7.6	1.5	7.6	1.4	8.0	1.5	8.9*	1.3
Lymphocyte count (/mm ³)	1.73	0.51	1.66	0.52	1.82	0.56	2.42*	0.59
Age (yrs)	69	8	66	9	66	7	61*	9
P.I.W. (%)	96	12	98	11	97	18	113*	11
P.W.L. (%)	9	12	5	6	6	7	3*	4
Duration (hrs.min)	2.47	1.15	2.47	0.94	2.41	0.77	3.31*	1.45
Perop. blood loss (ml)	700	670	830	1040	740	1030	1020	1440

*Pre- and peroperative parameters are not significantly different between the trial groups. P.I.W., duration of surgical procedure, and lymphocyte counts are in the non-depleted group significantly different from the values of the (depleted) trial groups. (*ANOVA $p < 0.05$)*

8.4.2 Complications

The immediate overall postoperative in hospital complication rate and mortality were not different between the 4 groups. In stage IV no major complications and 2 minor complications were observed in the non-depleted colorectal cancer patients, while in all other groups major complications were observed. Two patients in stage IV T.E.N. group died in the hospital and 3 others suffered major complications. No major complications occurred in the ND controls (table 8.3)(Chapter 6).

Table 8.3: Tumor stage and tumor spread

	TPN n=11	TEN n=7	depleted n=8	non-depleted n=6
TNM-classification				
20+	1	-	-	1
2++	1	1	1	3
30+	-	-	-	1
3++	4	-	4	1
40+	1	1	2	-
4+0	2	2	-	-
4++	2	3	1	-
Sexe				
Male	9	3	4	4
Female	2	4	4	2
Complication rate				
no	2	1	4	4
minor	6	1	3	2
major (mortality)	3 (1)	5 (2)	1 (1)	0 (0)

Tumor stage and tumor spread in stage IV colorectal cancer patients.

2/3/4 *T-stage*

. 0/+ *Negative/positive lymph nodes*

. 0/+ *Absence/presence of distant metastases*

In addition, sexe, localisation, and complication rates in stage IV colorectal trial groups are summarised. The number of patients in each cell is given. No statistically significant difference between the depleted trial groups is observed. In the non-depleted group there was a smaller tumor load as expressed by lower TNM-scores and no major complications were observed ($p<0.05$).

8.4.3 Survival

Overall survival at 90 months in the current study was 45%. The effect of perioperative nutritional support on survival of patients in all stages of disease is depicted for each trial group in figure 8.1. No difference in survival between nutritional support and control groups was seen.

Figure 8.1: The association of nutritional intervention with long term survival in colorectal cancer patients in all stages of disease. (log rank ns)

8.4.4 Stage I/II and III

As disease stage is the most prominent determinant of survival, separate analyses per stage were performed. Analyses for the separate stages I to III demonstrated no difference in mortality between study groups for nutritional intervention.

A stepwise Cox-regression analysis, deleting the least significant parameter step by step was performed for stage I/II, III and IV. The first column in table 8.4 summarises the results of the Cox regression for stage I/II disease. The second column shows the results for stage III-cancer patients. In both analyses perioperative blood loss showed an independent association with survival, as did hemoglobin levels in stage I and II. In stage III preoperative plasma albumin levels and total lymphocyte count also showed a significant association with survival.

8.4.5 Stage IV

Figure 8.2 displays the effect of perioperative nutritional support on survival of patients with stage IV-carcinoma. Curves of the depleted patient groups that

Figure 8.2: The association of nutritional support with long term survival of stage IV colorectal cancer patients. The curve of the depleted patients with nutritional intervention mimics the curve of the non-depleted control patients. The curves of the depleted patients receiving nutritional support differ significantly from the curve of the depleted patients without nutritional support. (log rank $p < 0.05$)

received parenteral ($n=11$) or enteral ($n=7$) nutritional support nearly mimic the curve of the non-depleted control patients ($n=7$). There is a significant difference between survival of the depleted control patients ($n=9$) and the survival of the non-depleted patients (log rank $p < 0.05$). Median survival of depleted control patients was 3 months, of enterally fed patients 7 months, of parenterally fed patients 7.5 months, while non-depleted control patients had a median survival of 8.5 months. The Cox-regression revealed in stage IV colorectal cancer patients a significant association with percent ideal body weight ($p < 0.05$), total lymphocyte count ($p < 0.05$) and perioperative nutritional support ($p < 0.05$) (table 8.4). Hemoglobin, albumin, or type of nutritional support were not significantly related with survival.

Table 8.4: Cox-regression model

Stage	I/II	III	IV		
	p	p	coeff/se	exp(coeff)	p
Preop. nutrit. support	ns	ns	-1.8195	0.3633	0.05
TPN/TEN	ns	ns	-	-	ns
blood loss	0.01	0.05	-	-	ns
Hemoglobin	0.01	ns	-	-	ns
Albumin	ns	0.01	-	-	ns
lymphocyte count	ns	0.05	1.9063	2.2079	0.05
PIW (<, > 95%)	ns	ns	-1.9653	0.2701	0.05
Postop. complications	ns	ns	-	-	ns
Sexe	ns	ns	-	-	ns

Results of Cox-regression model for each separate stage of disease. For stage I/II and stage III the significant parameters are shown by their p-value. For stage IV in the first column the estimated coefficients/standard error (coeff/se) or the z-statistics are given. The second column of data lists the relative risk estimate (exp(coeff)), while the last column lists the p-value of the likelihood ratio test for significance of the factor (after correction for the other factors).

Table 8.5 shows characteristics of all patients with stage IV carcinoma. They were comparable with respect to age, preoperative biochemical parameters, peroperative blood loss, tumor load and tumor spread. In addition, PIW, PWL and age were not different between trial groups. Tumor localisation, loco-regional tumor spread and pattern of distant metastases were not different between trial groups either (table 8.2). Non-depleted stage IV cancer patients, however, showed better preoperative parameters (table 8.2) and a smaller extent of tumor (table 8.3).

Table 8.5: Pre- and peroperative parameters stage IV colorectal cancer patients

Stage IV colorectal cancer	TPN n=11		TEN n=7		Depleted n=8		Non-depleted n=6	
	mean	range	mean	range	mean	range	mean	range
Total protein	68	5	68	8	71	7	74	5
Albumin	33	4	33	5	32	4	39	4
Pre-albumin	0.17	0.06	0.21	0.07	0.16	0.06	0.29*	0.06
Hemoglobin	7.0	1.6	6.8	1.7	7.5	1.7	8.9	0.9
Lymphocyte count	1.71	0.76	1.84	0.57	2.11	0.73	2.09	0.46
Age	69	9	70	7	68	5	61	8
P.I.W.	94	9	95	17	98	8	116*	6
P.W.L.	9	6	9	7	14	8	3*	4
Duration of procedure	2.23	1.39	2.49	0.95	2.16	0.80	2.4	1.5
Peroperative blood loss	568	488	871	821	637	1275	583	585

Pre- and peroperative parameters in stage IV colorectal cancer patients differ not significantly among the trial groups. The non-depleted reference group had significant better preoperative parameters ($p<0.05$).*

8.5 Discussion

The stage to which a malignancy of the GI tract has progressed is the most important determinant of survival. Other determinants of long term survival are indicators of depletion (Chapter 7). Whether correction of depletion by means of nutritional support is associated with enhanced tumor growth and, therefore, decreased survival in humans is not known. Only Weisdorf¹⁸ showed a positive effect of pre-treatment TPN on long term outcome of bone marrow transplantation patients.

Perioperative nutritional support of stage IV colorectal cancer patients who showed signs of depletion significantly prolonged survival, to a level similar to that of non-depleted control patients. These effects were not (yet) present in stage I, II, and III colorectal cancer patients.

It is known for some time that percentage weight loss and ideal body weight have prognostic value with respect to postoperative morbidity and mortality^{19,22},

and long term survival^{1,4,23}. In addition, total protein correlates significantly with long term survival²⁴.

Few studies have addressed the effects of other nutritional status parameters on long term survival^{1,4,5} and none the effect of perioperative nutritional support in this respect. Administration of routine T.P.N. as adjuvant to chemotherapy or radiation therapy has not resulted in a beneficial effect with respect to tolerance to therapy, morbidity, mortality or survival^{25,26}.

Suggestions that nutritional support would stimulate tumor growth, and consequently impair long term survival, have not been confirmed. A recent review concluded that no clinical evidence was present to support this suggestion²⁷.

Our observation that nutritionally supported stage IV cancer patients tolerated palliative surgical treatment better, as expressed by a significant improvement of long term survival, can not be explained by differences between study groups regarding type of operative procedure, degree of tumor spread or preoperative parameters. Perioperative morbidity data were also similar. We therefore must assume that this finding is truly associated with nutritional support.

8.6. Conclusion

We conclude from this study that in depleted patients with stage IV colorectal cancer perioperative nutritional support significantly improved long term survival.

The differences between the results of trials investigating the role of nutritional repletion as an adjuvant to chemotherapy, and the results of the studies by Weisdorf¹⁸ and our study, can be explained by the fact that nutritional repletion was given prior to the trauma.

The effect seems to be superior to even very aggressive systemic palliative treatment^{28,29}. A prospective randomised controlled trial to confirm our results is therefore warranted. Such a study offers the possibility to investigate mechanisms that may be causally related to our observation.

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Chapter 8

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Final discussion

9.1 Depletion parameters

As discussed in chapter 3 the goal of the assessment of the presence of depletion is to identify patients that are unable to stage a normal response to a disease or (surgical) trauma. This inability results in an additional risk in these patients for development of complications of their disease or of the treatment of their disease.

In the current study we used the Nutritional Index¹, developed in our hospital, for stratification of depletion. This index is composed of the parameters albumin, total lymphocyte count and percent ideal weight. Originally these parameters were thought to indicate malnutrition. However, at present we have good reasons to suggest that the nutritional index rather identifies depletion, resulting from metabolic stress.

Plasma albumin concentrations certainly correspond with the presence of metabolic stress. Plasma albumin concentrations were shown to be normal in long term starvation without presence of disease². But in patients with signs of sepsis, plasma albumin concentrations decrease within a few days, even in healthy young trauma patients. The clinical importance of plasma albumin concentrations is illustrated by the prognostic value for long term survival in GI cancer patients (as shown in chapter 7 & 8).

Total lymphocyte counts are also more affected by the presence of disease than by the presence of starvation, although few data are available regarding lymphocyte counts in starvation experiments. In septic conditions total lymphocyte counts decrease rapidly. Like plasma albumin concentrations, total lymphocyte counts were shown to have prognostic value in predicting survival of these cancer patients. The central role of the immune system in the natural history of cancer³ and in recurrence of cancer^{4,6} has since long been accepted.

Weight parameters are less clearly associated with metabolic stress. In starving conditions without presence of disease, weight is gradually decreasing. The loss of weight is principally body fat mass, used as energy source. Lean body mass is affected only slightly, because of protein sparing mechanisms during starvation. However, in the presence of disease and especially in septic conditions, not only body fat mass is affected, but specifically body cell mass decreases. This is reflected by negative protein balances, despite adequate (parenteral) nutrition.

Weight loss is in these conditions often masked by increasing extracellular water.

Weight loss, therefore, reflects both starvation and disease. It has been suggested that the assessment of fat free mass, or loss of fat free mass more accurately defines the presence of depletion. Fat free mass is currently fairly easily measured by impedance techniques in healthy individuals, albeit that validation in various (septic) disease conditions is only in its early phase. The accumulation of extracellular water may jeopardise the validity of the technique.

9.2 Prerequisites of trials

In chapter 4 the prerequisites are defined that should be met in trials investigating the effect of nutritional therapy.

- Nutritional status parameters should identify a patient group that is relevant. According to the index we used to identify patients as depleted, about three-quarter of the study population was depleted. It is, therefore, likely that these criteria were too mild. The absence of clear-cut answers in chapter 6 may be the result of this phenomenon. Subanalysis of the severely depleted patients where a positive effect of preoperative nutrition on the incidence of postoperative complications was observed, underlines this point.

- Advance calculations should define the group size required to reach significance of the expected differences. Interim analyses are necessary to avoid treatment which has already been shown to be inferior to the other treatment. Interim analyses after admitting 201 patients in our study revealed no benefit for one of both nutritional intervention therapies. Consequently, the trial was discontinued at that moment. One of the possible explanations for the absence of significant effects is that all major complications were analysed as one group. The group of major complications encompasses a variety of complications, including some which are not believed to be influenced by nutritional therapy. Detailed analyses showed, as reported in chapter 6, and in some other trials in the literature, a benefit of nutritional therapy in the severely depleted patient group. However, the number of patients in this group is rather small.

9.3 Nutritional intervention

As shown in chapter 5, factors indicating depletion influence the severity of complications. It seems as if in depleted patients minor complications will progress to a major complication more often or a major complication will result

in a sequence of multiple complications. The capability to respond to intrusions is only in part dependent on 'nutritional status', and nutritional support, therefore, can only partly influence or modify outcome of therapy. Depletion increases the risk of perioperative complications, but not to the extent that all depleted patients develop complications. Similarly it is unreasonable to expect complete eradication of all postoperative complications by nutritional support. The acknowledgement of the limited role of depletion in the development of postoperative complications, and the difficulty to demonstrate nutritional support as effective therapy in reducing complications illustrates that the expectations of the effects of nutritional therapy in the past two decades were too high.

In this study we confirm the hypothesis that *preoperative* nutritional therapy supports severely depleted patients with a significant reduction of postoperative complications. This intervention must contain sufficient amounts of nutrients and must last a sufficient time period. Nearly all trials supporting patients shortly before or only after operation, failed to demonstrate positive effects of nutritional therapy. It is warranted to extend the conclusions of this study to other situations where severely depleted patients are subjected to (aggressive) therapy: pre-treatment nutritional support could also have beneficial effects in other treatment modalities. However, the option of nutritional intervention prior to chemotherapy and radiation therapy has not been tested. None of the studies concerning nutritional therapy in these two treatment modalities showed a beneficial effect if given during or after the treatment therapy had started.

9.4 Survival

Long term survival is first of all influenced by stage of disease. Apart from this, depletion related parameters, like ideal weight, plasma albumin levels and preoperative hemoglobin values, showed a significant association with long term survival. 'Correction' of these parameters by preoperative nutritional support failed to show beneficial effects in the total group. This is probably due to the stage to which the disease has progressed, and, as explained above, the relative role of depletion and rather mild inclusion criteria for the trial. However, preoperative nutrition did not show any adverse effects on long term survival.

Analysis per stage of disease showed beneficial effects of preoperative nutrition in stage IV colorectal cancer disease. The discontinuation of the study is responsible for the small number of stage IV colorectal cancer patients as described in chapter 8. In such a small patient group (34 patients) it is difficult to draw firm conclusions concerning the influence of nutritional therapy on long

term survival. To address this question a multicenter trial should be initiated, confirming the strong suggestions of a positive effect on long term survival of nutritional intervention in depleted patients with advanced stages of cancer.

9.5 Blood loss

Blood loss was shown to be of major importance in predicting outcome of therapy. Loss of more than 500 ml of blood was highly correlated with the presence of postoperative complications. Because of the correlation and the improved outcome of surgical therapy after nutritional repletion in depleted patients that lost over 500 ml of blood, one should like to take blood loss into account when making decisions with regard to the start of nutritional support. But, more than an preoperative estimate of blood loss is not possible.

Blood loss probably also reflects the need for blood transfusion. Both loss of blood and transfusion of blood have been claimed to have detrimental effects on the immune system resulting in a variety of immunosuppressive actions⁷⁻¹² and decreased survival¹³⁻¹⁹. Accepting very low hematocrit values has not been shown detrimental, and the effect of transfusions of homologous blood products as opposed to heterologous blood products is currently under investigation. Of course blood loss during surgical procedures should be kept to a minimum during surgical procedures. This is common practice to every surgeon. It is not yet known which blood component(s) induce(s) the immunosuppressive effect. It is certainly not always necessary to replenish volume deficits with whole blood. It is not yet established if replenishment of volume deficits with other products will have less detrimental effects.

Further investigations are necessary to explain the claimed detrimental effects of transfusions on survival: are they caused by transfusion itself, or are these detrimental effects an epiphenomenon of other confounding effects such as the size of the tumor, vascularisation of the tumor, resectability and site of the tumor, duration and extension of surgical procedure or surgical skill.

9.6 Clinical implication

The results of the trial described in this thesis have resulted in policy changes in day-to day clinical practice: depleted patients showing a recent weight loss of more than 10% receive preoperative nutritional support. In this group of severely depleted patients we demonstrated that postoperative complications are reduced, and the severity of complications is limited.

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Summary

Malnutrition or depletion has since long been associated with an increased incidence of mortality and morbidity of surgical therapy. The fact that depleted patients develop more postoperative septic complications requires careful preoperative detection of depletion. There is no agreement, however, in the literature how depletion should be detected and which parameters of depletion are most predictive of the development of postoperative complications. The confusion is evenmore increased because the relative contribution of all potential conceivable risk factors has never been assessed together. If depletion indeed has an independent, substantial influence on surgical outcome, then repletion might improve outcome. The magnitude of these improvements are depending of the impact of depletion on outcome of surgical trauma. Therefore, if nutritional support effectuates in improved tissue and organ functioning it is a tool to reverse depletion, and consequently to improve outcome of surgical therapy. This concept has been the basis of perioperative nutritional support.

Aim of this thesis was to analyse surgical riskfactors together and weighing their relative contribution on postoperative complications and long term survival. The influence of perioperative nutrition was analysed on short term effects on postoperative complications and long term effects on survival.

When patients are metabolically stable, body composition is kept constant over longer periods of time through maintenance of a balance between intake and losses of energy, protein, and other essential nutrients. Deficiencies are the result of a derangement of the balance, either on the intake side or on the expenditure side, and lead to changes in body composition and disturbed organ functioning.

Nutritional assessment signifies detection of abnormal body composition and organ function resulting from *insufficient nutritional intake*; including energy and protein intake, and intake of other essential nutritients.

However, the actual intake of energy, protein and other nutrients by depleted patients is not always decreased. Some studies in cancer patients revealed a normal food intake compared to a control group. Nutritional assessment in these patients is used to detect abnormal body composition and disturbed organ function resulting from *increased loss*: increased energy expenditure, increased protein degradation, increased loss of total body nitrogen, and increased loss of essential nutrients, result of metabolic derangements. In most cases a mixture of

both conditions is present, both resulting in depletion. The recognition that depletion has a nutritional origin and a metabolic origin may explain why nutritional intervention is not always successful in reversing 'malnutrition'. The metabolic side of depletion is probably not easily reversed with 'ordinary' nutritional intervention.

The broad interest in the field of nutrition has resulted over the past two decades in a considerable number of publications, demonstrating that aberrations of nutritional status parameters are risk factors for surgical outcome. Many individual nutritional status parameters have been suggested to describe depletion and the degree of malnutrition. Many of these parameters show a significant correlation with postoperative morbidity and mortality and are therefore often used to calculate the risk for development of postoperative complications. In monofactorial analyses these parameters showed a fair to good correlation with the incidence of postoperative complications. But no single indicator has been proven better than any other. Combination of parameters has not been shown to increase sensitivity, reliability and applicability for the individual patient because of the high degree of correlation among variables. Indices, derived from multiple variate regression analyses, combining anthropometric, biochemical, and immunological measurements, did not show a further improvement either. The lack of a gold standard, and the index being developed in a specific patient group, explains why the results of application of these indices to other patient groups are so disappointing. Because of the way patients are selected when indices are established, not only the influence of depletion is considered, but also the influence of the underlying disease on outcome of surgical therapy. In addition, indices are frequently only composed of parameters, that are traditionally thought to be associated with depletion. As a consequence the role of nutrition related risk factors has been overemphasised, distracting the attention from the role that disease related factors and surgical therapy play in the development of postoperative complications. The outcome of surgery is the result of many factors e.g. patient related factors, including depletion, but also extent and type of the surgical procedure, skill of the surgeon, and the underlying disease itself.

Depletion increases the risk of perioperative complications, but not to the extent that all depleted patients develop complications. It is, therefore, unreasonable to expect complete eradication of all postoperative complications by nutritional support.

The attractiveness of the association of nutritional depletion with postoperative complications has always been the suggestion that depletion can be treated, in

contrast to many other risk factors. This has led to high expectations of the ability of nutritional intervention to decrease morbidity and mortality from surgical therapy. These expectations were, as we know now, too high. Firstly it gradually became clear that most parameters thought to represent depletion and depletion associated surgical risk represent the presence of metabolic stress. Secondly, subsequent trials investigating the effect of nutritional intervention on outcome of surgical therapy, almost invariably failed to produce a positive result. Reasons for this failure include the fact that most trials do not fulfil the minimum criteria with regard to design and number of randomised patients. A further criticism is that in most trials the criteria that designate patients as 'malnourished' are rather mild and that non-depleted patients are not excluded from randomisation. In most studies surgery was not performed in the control group a few days after admission. These patients were left on a normal hospital diet, sometimes resulting in starvation. Furthermore, patients admitted for elective minor surgery as well as cancer patients undergoing extensive surgery were included.

In this thesis we determined the additional risk that originates from an abnormal nutritional status, depletion parameters, in addition to other well accepted surgical risk factors were analysed prospectively, for their association with postoperative complications. Other risk factors included type and duration of the surgical procedure, surgical skill, peroperative blood loss, type and stage of the disease, age of the patient, and the presence of coexisting diseases. Nearly all parameters in this study showed in monofactorial analyses (ANOVA or Chi-Square) a significant correlation with outcome, as has also been shown in literature. However, a multiple logistic regression analysis, with complication rate as dependent factor, revealed peroperative blood loss to be the most important factor associated with the development of postoperative complications. In addition, age was significantly associated with the occurrence of postoperative complications. When a complication occurred, percentage ideal weight and duration of the operative procedure were associated with the severity of the complication. Parameters reflecting the presence of metabolic stress, e.g. albumin, did not show an independent association with the development of postoperative complications. The results of this study suggest that repletion diminishes the severity of complications, rather than preventing their development.

We therefore undertook a prospective randomised trial to investigate the effects of at least 10 days preoperative total parenteral nutrition (n=51) or total enteral nutrition (n=50), on the rate of major postoperative complications or mortality

in a homogeneous patient group with signs of depletion. Fifty patients served as a depleted control group and 49 patients served as a non-depleted reference group and were operated without delay.

Depleted control patients suffered significantly more septic complications than patients in the non-depleted reference group ($p < 0.05$). There was no significant difference, however, in septic complications between either of the nutritional support groups and the non-depleted control group. In high risk patients, with weight loss $> 10\%$ of body weight and over 500 ml blood loss during operation, a significant decrease ($p < 0.05$) in major complications was observed as a result of nutritional support.

The results of our nutritional intervention trial in a homogeneous cancer patient group, suggest a benefit with fewer episodes of sepsis and less intra-abdominal abscess formation. This effect was more pronounced in the more severely depleted patients and was not obtained at the cost of increased morbidity of the nutritional support technique itself. We conclude that preoperative nutritional support in patients with severe depletion, results in a reduction of major complications to a degree that justifies its routine use in the selected group of patients with signs of severe depletion (i.e. weight loss $> 10\%$) prior to surgery.

In addition, the effect of depletion parameters on long term survival was analysed to assess whether the association between depletion and decreased survival of gastric or colorectal cancer patients is independent from tumor stage. Stage of disease, preoperative percent weight loss, percent ideal body weight, plasma protein, plasma albumin, plasma pre-albumin concentration and blood loss were significantly correlated with long term survival (Kaplan-Meier, log rank $p < 0.05$) in both gastric and colorectal cancer. No adverse effects of perioperative nutrition on long term survival were seen.

A Cox multiple variate analysis with survival as dependent variable yielded, besides stage of disease, independent effects of percent ideal body weight, plasma albumin values and blood loss. Although it has long been thought that the association of weight loss and low plasma albumin levels with long term survival reflects progressing tumor stages, we now demonstrate this phenomenon to be independent from tumor stage. It is possible that weight loss and cachexia are epiphenomena of the metabolic relation between host and tumor. We conclude that depletion has an adverse effect on long term survival of patients with gastric or colorectal carcinoma, that is independent from the stage of disease.

The effects of perioperative nutrition on tumor growth and long term survival of GI tract cancer patients have not been documented. Whether correction of

depletion by means of nutritional support is associated with enhanced tumor growth and, therefore, decreased survival in humans is not known. Administration of routine T.P.N. as adjuvant to chemotherapy or radiation therapy has not resulted in a beneficial effect with respect to tolerance to therapy, morbidity, or survival. In 149 consecutive patients (62 females, 87 males) admitted for surgical treatment of newly detected colorectal cancer the long term effect of perioperative nutrition was analysed. Depleted patients in stage IV colorectal cancer survived significantly shorter than non-depleted stage IV cancer patients. Depleted stage IV colorectal cancer patients receiving perioperative nutritional support survived significantly longer than depleted patients who received no nutritional support (log rank $p < 0.05$). Such effects were not observed in stage I, II and III. In a Cox multivariate regression analysis this beneficial effect of perioperative nutrition showed to be an independent observation.

We therefore conclude that perioperative nutritional support improved long term survival after surgical treatment in stage IV colorectal cancer patients. This effect can not be explained by differences between study groups regarding type of operative procedure, degree of tumor spread or preoperative parameters. We must assume, therefore, that this finding is truly associated with nutritional support.

In daily practice, the results of this thesis have led to policy changes in clinical preoperative care of depleted (cancer) patients. In patients with weight loss over 10% of usual body weight, 10 days of preoperative nutritional support is indicated, provided the surgical treatment can be delayed without adverse effects. The results of this trial may possibly be extended to all depleted surgical patients. The finding that perioperative nutritional support improves long term survival in depleted stage IV cancer patients needs confirmation in a larger trial.

Samenvatting

Depletie is sinds lang geassocieerd met een verhoogde incidentie van postoperatieve chirurgische complicaties en mortaliteit.

Het feit dat een gedepleerde patiënt meer postoperatieve complicaties ontwikkelt, maakt een goede preoperatieve evaluatie van depletie noodzakelijk. Er is echter in de literatuur geen consensus over hoe depletie moet worden gedetecteerd en welke parameters de grootste predictieve waarde hebben bij het voorspellen van postoperatieve complicaties. De verwarring wordt nog vergroot doordat de onderlinge relatie van al deze parameters nog nooit is bekeken. Als het zo is dat depletie een onafhankelijke, substantiële invloed heeft op het postoperatieve beloop, dan moet repletie het beloop verbeteren. De mate waarin dit zal gebeuren is afhankelijk van de invloed van depletie op het postoperatieve beloop. Als perioperatieve voeding een middel is om depletie te verminderen en daarmee leidt tot een verbetering van orgaanfuncties, dan zou perioperatieve voeding het chirurgische resultaat verbeteren kunnen. Dit concept is de basis geweest van perioperatieve voedingstherapie.

Het doel van deze studie was het analyseren van chirurgische risicofactoren, om hun onderlinge samenhang en ieders individuele invloed op postoperatieve complicaties en lange termijn effecten vast te stellen.

In metabool stabiele patiënten is de lichaamssamenstelling over langere tijd constant. Er is een balans tussen inname en verlies van energie, eiwitten en andere nutriënten. Deficiënties treden op als er een dysbalans ontstaat tussen enerzijds de inname en anderzijds de verliezen. Een langer durende disbalans leidt tot veranderingen in lichaamssamenstelling en verstoorde orgaanfunctie.

‘Nutritional assessment’ betekent het vaststellen van de voedingstoestand en abnormale lichaamssamenstelling van een patient als resultaat van een *verminderde inname* van voedingsstoffen, van zowel energie, eiwit als andere essentiële nutriënten. Echter langdurige honger kan door een gezonde persoon langdurig volgehouden worden, zonder dat dit leidt tot grote veranderingen in lichaamssamenstelling.

De inname bij gedepleerde patiënten is niet altijd afgenomen. Sommige studies toonden een normale voedselinname aan bij gedepleerde kankerpatiënten. Het vaststellen van een abnormale lichaamssamenstelling onder deze omstandigheden bij gedepleerde patiënten met een normale inname, is het vaststellen van metabole ontregelingen door *toegenomen verliezen* van energie, eiwit en

andere essentiële nutriënten.

Omdat de term 'ondervoeding' vaak alleen de innamezijde belicht is het beter te spreken over depletie, een term die beide oorzaken dekt. Het erkennen van de twee oorzaken van depletie, verklaart ook al waarom voedingstherapie niet altijd succesvol is in het omkeren van 'ondervoeding'. In ziekte is er bijna altijd een combinatie van beide condities, waardoor er een abnormale of verminderde respons op ziekte ontstaat. Deze veranderde respons vormt een additioneel risico voor het ontwikkelen van complicaties. Het is echter niet synoniem voor de ontwikkeling van complicaties of synoniem voor een gestoord postoperatief beloop. De metabole kant van depletie zal door de normale voedingsondersteuning niet gemakkelijk verholpen worden. Zo zal een gedepleerde patiënt met een morbus Crohn met chronische activiteit en septicemie niet herstellen van depletie zolang de actieve infectie met metabole en hormonale veranderingen niet verholpen is. Een vergelijkbaar gedepleerde patiënt met een stenose van de darm op basis van zijn morbus Crohn, zonder actieve ontsteking, zal daarentegen met voedingstherapie snel herstellen van zijn depletie.

In de literatuur zijn er de laatste twee decennia vele publicaties verschenen die aantonen dat afwijkingen in de parameters van de 'voedingsstatus' geassocieerd zijn met postoperatieve complicaties. In monofactoriële analyses hebben de meeste van deze parameters een redelijke tot goede correlatie met de incidentie van postoperatieve complicaties. Niet één van die afzonderlijke factoren had echter een bewezen betere predictieve waarde. Bovendien zijn er bijna geen patiënten zonder minstens één abnormale waarde voor alle in de literatuur genoemde parameters. Dat leidde tot de ontwikkeling van velerlei indices met een combinatie van antropometrische, biochemische en immunologische parameters. Deze indices, veelal gebaseerd op regressieanalyses, lieten echter geen toename van sensitiviteit, betrouwbaarheid of toepasbaarheid zien. Dit komt mede door de hoge correlaties tussen de gebruikte parameters. Het ontbreken van een gouden standaard en het feit dat de index in een specifieke patiëntengroep ontwikkeld is, verklaart al grotendeels de matige resultaten van de indices, wanneer deze toegepast worden op een andere patiëntengroep. Door die patiëntenselectie meten deze indices niet alleen het effect van depletie, maar tevens de invloed van de onderliggende ziekte op de uitkomst van chirurgische therapie. Meestal bevatten deze indices alleen parameters die geassocieerd zijn met depletie. Dit legt een te grote nadruk op depletie. Die nadruk leidt de aandacht af van de rol die ziekte en andere therapie-gerelateerde factoren hebben op het postoperatieve beloop. Depletie is echter maar één van de vele factoren voor het uiteindelijke resultaat, naast vele andere factoren, die minstens zo belangrijk zijn. De rol van die andere factoren werd vergeten of ontkend.

Om de predictieve waarde van indices te vergroten moesten er ook andere factoren meegenomen worden, die van invloed zijn op het postoperatieve beloop. Zulke factoren zijn de leeftijd van de patiënt, coëxistente ziekten, de duur en de uitgebreidheid van een ingreep, het peroperatieve bloedverlies, het soort anesthesie en de vaardigheid van de chirurg. Depletie is maar één van de risico-factoren voor de uitkomst, van zowel chirurgische, chemotherapeutische als radiotherapeutische therapie. Voedingsinterventie zal daarom ook slechts gedeeltelijk de uitkomst kunnen beïnvloeden. Dit verklaart voor een deel de tegenvallende resultaten van voedingsinterventietrials. Depletie vergroot het risico op postoperatieve risico's, maar niet in die mate dat alle gedepleerde patiënten een complicatie ontwikkelen. Het is dan ook niet te verwachten dat door middel van voedingstherapie de postoperatieve complicaties grotendeels voorkomen kunnen worden.

Het aantrekkelijke van een sterke samenhang tussen de voedingstoestand en postoperatieve complicaties is het idee dat de voedingstoestand door middel van voedingstherapie beïnvloed kan worden, in tegenstelling tot vele andere factoren. Dit heeft geleid tot veel te hoog gespannen verwachtingen van het effect van voedingstherapie met betrekking tot het terugdringen van postoperatieve morbiditeit en mortaliteit. Dat deze verwachtingen gestoeld waren op verkeerde uitgangspunten, blijkt uit het feit dat de meeste parameters die gebruikt werden ter identificatie van voedingstoestand steeds meer gezien worden als indicatoren van metabole stress. De opeenvolgende interventietrials faalden nagenoeg allen in het geven van een éénduidig antwoord door conceptuele en methodologische fouten. De grootste kritiek op de meeste trials is dat de niet-gedepleerde patiënten niet uitgesloten werden van randomisatie. Gebeurde dit wel, dan waren de exclusiecriteria in het algemeen zeer mild. De controlegroepen ondergingen in veel gevallen niet de standaardbehandeling, maar werden preoperatief even lang in het ziekenhuis gehouden als de interventiepatiënten, zonder een adequate registratie van hun inname. Verder was de patiëntenpopulatie in het algemeen zeer divers met uiteenlopende opnameindicaties, variërend van electieve herniachirurgie tot uitgebreide thoraco-abdominale procedures. Het nagestreefde doel van een reductie van postoperatieve complicaties tot wel 50% in sommige studies demonstreert nog eens de veel te hoge verwachtingen van voedingstherapie.

In een studie van 172 maag- en darmkanker patiënten maakten wij een analyse van de depletie-parameters, tesamen met het effect van andere geaccepteerde chirurgische risico-factoren, zoals coëxistente ziekten, de leeftijd van de patiënt, de vaardigheid van de chirurg en het peroperatieve bloedverlies. Alle geanalyseerde depletieparameters hadden in monofactoriële analyses een goede

correlatie met postoperatieve complicaties. Echter in een stapsgewijze regressieanalyse met postoperatieve complicaties als afhankelijke variabele bleek bloedverlies een zeer significante onafhankelijke associatie te hebben met de postoperatieve complicaties. Daarnaast was ook de leeftijd van de patiënt een factor die significant geassocieerd was met de postoperatieve complicaties. Als er een complicatie opgetreden was, waren de duur van de operatie en het percentage ideaal gewicht geassocieerd met de ernst van de complicatie.

De resultaten van deze studie suggereren dat de uitgebreidheid van een procedure, weergegeven door het peroperatieve bloedverlies en de duur van de operatie, en de leeftijd van de patiënt, geassocieerd zijn met het optreden van een postoperatieve complicatie. Hiernaast zijn de depletieparameters, zoals weergegeven door het percentage gewichtsverlies en het percentage ideaal gewicht, geassocieerd met de ernst van een complicatie.

In de interventie-trial werden 151 patiënten met een bewezen maag of colorectale maligniteit gerandomiseerd, die op basis van een index ondervoed genoemd konden worden. Een-en-vijftig patiënten werden gerandomiseerd voor parenterale voeding, vijftig patiënten werden gerandomiseerd voor enterale voeding, welke beiden gedurende 10 dagen preoperatief gegeven werd. Vijftig patiënten werden gerandomiseerd als controlegroep en werden zonder uitstel geopereerd. Negen-en-veertig patiënten waren volgens de criteria niet ondervoed. Zij werden niet gerandomiseerd en fungeerden als goedgevoede referentiegroep. De postoperatieve complicaties werden aan de hand van de ernst van de complicatie gescoord als geen complicatie, een geringe complicatie of een ernstige complicatie. Septische abdominale complicaties zoals intra-abdominale abcessen en sepsis traden in de ondervoede patiënten duidelijk frequenter op dan in de goedgevoede referentiegroep. De beide voedingsondersteunde trialgroepen lieten een afname van deze complicaties zien. In de ondervoede controlegroep kwamen significant meer multipale complicaties voor. In de ernstig gedepleerde patiëntengroepen met een percentage ideaal gewicht van 95% of lager was het effect van voeding nog nadrukkelijker met een significant verhoogd aantal septische complicaties in de gedepleerde controlegroep. In de groep patiënten met een peroperatief bloedverlies van meer dan 500 ml werden minder abcessen en sepsis gezien in de beide voedingsondersteunde groepen ten opzichte van de gedepleerde controlegroep. We concluderen uit deze studie dat het routinematig geven van perioperatieve voeding in ondervoede maag- en darmkankerpatiënten met tekenen van ernstige depletie, een voordelig effect heeft. Septische en abdominale, infectieuze complicaties hebben een verlaagde incidentie in de voedingsondersteunde groepen. Deze resultaten rechtvaardigen routinematige preoperatieve voeding

bij ernstig gedepleerde patiënten, met name in die groep die bij opname een gewichtsverlies heeft van meer dan 10 % van hun gebruikelijke gewicht.

Tevens werd het effect van depletieparameters op de overleving nagegaan om te analyseren welke invloed depletie op survival heeft, onafhankelijk van tumorstadium. Het stadium van de ziekte, het preoperatieve percentage gewichtsverlies, het percentage ideaal gewicht, totaal plasma-eiwit, plasma-albumine, plasma-prealbumine en peroperatief bloedverlies waren significant gecorreleerd met de overleving in Kaplan-Meier analyses (log rank $p < 0,05$) van zowel maagkanker als van colorectale tumoren. *Er werden geen nadelige effecten van voeding gezien op de overleving.* Een Cox regressieanalyse liet naast de invloed van het stadium van de ziekte, een onafhankelijk effect op de overleving zien van het percentage ideaalgewicht, het plasma-albumine gehalte en het peroperatieve bloedverlies. Hoewel lang gedacht is dat het gewichtsverlies en een laag plasma-albumine epifenomenen van een gevorderd tumorstadium waren, toonden we aan dat deze parameters een effect op overleving hebben, onafhankelijk van tumor stadium. Het gewichtsverlies, de cachexie en het albumine zijn mogelijk een uiting van de metabole relatie tussen gastheer en tumor.

We concluderen uit deze studie dat depletie een nadelig effect heeft op de overleving van gastro-intestinale kankerpatiënten, welke onafhankelijk is van het stadium van de ziekte.

De effecten van perioperatieve voeding op tumorgroei en overleving zijn niet beschreven. Een versnelde tumorgroei en gereduceerde overleving bij mensen is niet beschreven. Het routinematig geven van (parenterale) voeding als adjuvans bij chemotherapie of bestralingstherapie hebben niet geresulteerd in een verbeterde tolerantie van therapie, morbiditeit, mortaliteit en overleving. Bij 149 opeenvolgende patiënten (62 vrouwen, 87 mannen) opgenomen voor de chirurgische behandeling van een colorectale tumor, werd het lange termijn effect van perioperatieve voeding onderzocht. Gedepleerde, stadium IV colorectale kankerpatiënten hadden een significant kortere overleving als niet gedepleerde patiënten. Gedepleerde, stadium IV colorectale kankerpatiënten, die perioperatieve voeding ontvingen, leefden significant langer dan gedepleerde patiënten zonder perioperatieve voeding (log rank $p < 0,05$). Er werden geen verschillen gevonden ten aanzien van de tumorlocalisatie, de grootte van de tumor, de leeftijd van de patiënt, het geslacht, en de pre-operatieve depletieparameters. In stadium I, II en III werden deze verschillen niet gevonden. Een Cox-regressie analyse toonde aan dat dit voordelige effect in stadium IV onafhankelijk was van andere factoren.

We concluderen hieruit dat perioperatieve voeding een voordelig effect heeft op de overleving van gedepleerde, stadium IV colorectale kankerpatiënten.

De resultaten van dit proefschrift hebben geleid tot veranderingen in het pre-operatieve klinische beleid in het AZM. Gedepleerde patiënten, die een grote geplande ingreep moeten ondergaan, en die een gewichtsverlies van meer dan 10% van hun normale lichaamsgewicht vertonen, worden 10 dagen preoperatief gevoed, vooropgezet dat uitstel van de operatie verantwoord is. De bevinding dat perioperatieve voedingsondersteuning in gedepleerde, stadium IV colorectale kankerpatiënten tot een verbeterde overleving leidt, zal in een grotere trial bevestigd moeten worden.

APPENDIX 1

DAY	A																	OK
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
BLOOD																		
Hb, Ht	X			X					X				X				X	
W.B.C.	X			X					X				X				X	
E.S.R.	X			X					X				X				X	
Na ⁺	X			X					X				X				X	
K ⁺	X			X					X				X				X	
Cl ⁻	X			X					X				X				X	
Ca ⁺⁺	X			X					X				X				X	
Alk.Res.	X			X					X				X				X	
PO ₄ ⁻	X			X					X				X				X	
Urea	X			X					X				X				X	
Creatinin	X			X					X				X				X	
A. Phos.	X			X					X				X				X	
γGTP	X			X					X				X				X	
ASAT	X			X					X				X				X	
ALAT	X			X					X				X				X	
LDH	X			X					X				X				X	
Bili. and (%)	X			X					X				X				X	
Protein	X			X					X				X				X	
Albumin	X			X					X				X				X	
Pre-albumin	X			X					X				X				X	
T.I.B.C.	X			X					X				X				X	
T.L.C.	X			X					X				X				X	
Glucose	X				X				X					X			X	
Folic acid	X								X						X		X	
Vit. B12	X								X							X	X	
Cu ⁺⁺	X								X								X	
Zn ⁺⁺	X								X								X	
Mg ⁺⁺⁺	X								X								X	
TRP	X								X								X	
Amino acids	X								X								X	
F.F.A.	X								X								X	

Appendix I

DAY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
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GENERAL

Tension	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fluid balance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
diet anamnesis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

DAY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
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URINE

Amount	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
total K	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Glucose	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total N	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3-MH	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creat.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Density	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

A: admittance
 OK: day of operation
 TRP: tryptophan
 FFA: free fatty acids
 3-MH: 3 methyl-histidin

APPENDIX 2

TNM Classification Gastric Cancer

Primary Tumor (T)

- T_x Minimum requirements to assess the primary tumor cannot be met.
- T₀ No evidence of primary tumor.
- T_{is} Tumor limited to the mucosa without penetration into the lamina propria.
- T₁ Tumor limited to mucosa or mucosa and submucosa regardless of its extent.
- T₂ Tumor involves mucosa and the submucosa (including the muscularis propria), and extends to or into the serosa but does not penetrate through the serosa.
- T₃ Tumor penetrates through the serosa without invading contiguous structures.
- T_{4a} Tumor penetrates through the serosa and involves immediately adjacent tissues, such as lesser omentum, perigastric fat, regional ligaments, greater omentum, transverse colon, spleen, esophagus, or duodenum by way of intraluminal extension.
- T_{4b} Tumor penetrates through the serosa and involves the liver, diaphragm, pancreas, abdominal wall, adrenal glands, kidney, retroperitoneum, small intestine or esophagus, or duodenum by way of of serosa.

Nodal Involvement (N)

- N_x Minimum requirements to assess the regional lymph nodes cannot be met.
- N₀ No metastases to regional lymph nodes.
- N₁ Involvement of perigastric lymph nodes within 3 cm of the primary tumor along the lesser or greater curvature.
- N₂ Involvement of the regional lymph nodes more than 3 cm from the primary tumor, which are removed or removable at operation, including those located along the left gastric, splenic, celiac, and common hepatic arteries.
- N₃ Involvement of other intra-abdominal lymph nodes, such as the para-aortic, hepatoduodenal, retropancreatic, and mesenteric nodes.

Distant Metastasis (M)

- M_x Minimum requirements to assess the presence of distant metastasis cannot be met.
- M₀ No (known) distant metastasis.
- M₁ Distant metastasis present.

Stage grouping

- Stage 0 T_{is}, N₀, M₀
- Stage I T₁, N₀, M₀
- Stage II T₂, T₃, N₀, M₀
- Stage III T₁-T₃, N₁-N₂, M₀
T_{4a}, N₀-N₂, M₀
- Stage IV T₁-T₃, N₃, M₀
T_{4b}, any N, M₀
any T, any N, M₁

TNM Classification Colon and Rectal Cancer

Primary Tumor (T)

- T_x Minimum requirements to assess the primary tumor cannot be met.
 T₀ No evidence of primary tumor.
 T_{is} Tumor limited to the mucosa without penetration into the lamina propria.
 T₁ Tumor limited to mucosa or mucosa and submucosa regardless of its extent.
 T₂ Tumor involves mucosa and the submucosa (including the muscularis propria), and extends to or into the serosa.
 T_{3a} Tumor with extension beyond colon to immediately contiguous structures, without fistula formation.
 T_{3b} Tumor with extension beyond colon to immediately contiguous structures, with fistula formation.
 T₄ Tumor extending beyond the immediately adjacent organs or tissues.

Nodal Involvement (N)

- N_x Minimum requirements to assess the regional and/or juxta regional lymph nodes cannot be met.
 N₀ No metastases to regional lymph nodes.
 N₁ Evidence of involvement of regional lymph nodes.
 N₄ Evidence of involvement of juxta-regional lymph nodes
 N₂ and N3 are not applicable.

Distant Metastasis (M)

- M_x Minimum requirements to assess the presence of distant metastasis cannot be met.
 M₀ No (known) distant metastasis.
 M₁ Distant metastasis present.

Stage grouping

- Stage 0 Tis, N₀, M₀
 Stage I T₁, N₀, M₀
 Stage II T₂, T_{3a}, N₀, M₀
 Stage III T₁-T_{3b}, N₁, N₄, M₀
 T₄, N₀, N₁, N₄, M₀
 Stage IV T₁-T_{3b}, N₄, M₀
 T₄, any N, M₀
 any T, any N, M₁

Slechts verwondering?

Veel waardevolle zaken als relaties, hobbies, studie, boeken, etcetera hebben de laatste jaren moeten wijken voor dit onderzoek. Gelukkig is er tijd gebleven voor verwondering.

Verwondering?

Hoezo?

Het belangrijkste wat je leert tijdens het proces van promoveren is dat je je gaat verwonderen over relaties. Je gaat vraagtekens zetten bij allerlei verbanden. Zijn relaties wel zo absoluut als ze lijken?

Het wordt je geleerd je hersenen te trainen in het leggen van relaties en verbanden. Verbanden die je doen verwonderen en verbazen. Je beseft dat er zo veel is dat je niet weet. Die grote hersenen, vol met informatie, die relaties zoeken tussen allerlei gegevens en zich verwonderen over verbanden die er lijken te bestaan of zouden kunnen bestaan. Relaties tussen punten van een grafiek en de individuele patiënt, tussen de resultaten van dit boekje en de klinische praktijk. Die verwondering gaat ook buiten het onderzoek door: relaties tussen een boom en een auto, tussen de samenhang van de verhoudingen in de opbouw van een kathedraal en religie, etcetera. Voor ieder individueel van ons zijn die relaties vaak zo absoluut en zo waar, een individuele wijsheid, eigen-wijsheid. Maar van iedere relatie of van iedere eigen-wijsheid is het tegendeel evenzeer waar.

Je gaat je eigenlijk steeds meer verbazen over al die wonderbaarlijke relaties die er tussen de dingen lijken te bestaan. Door je op een wetenschappelijke manier te verwonderen, bepaal je niet alleen je eigen standpunt opnieuw, maar maak je jouw wijsheid ook voor anderen inzichtelijk.

Peter en Maarten, het bijbrengen van dit inzicht en het wegwijzen maken hierin zonder dat je blijft steken in slechts verwondering, beschouw ik als jullie grootste bijdrage aan mijn wetenschappelijke vorming en dit boekje. Heel erg veel dank hiervoor.

Verder wil ik allen die op enigerlei wijze hebben bijgedragen aan het tot stand komen van dit proefschrift hartelijk danken. Met name wil ik hierbij noemen Resi Buil-Maassen en Margriet Rouflart die het vergaren van de data voor het overgrote deel voor hun rekening hebben genomen.

Curriculum vitae

Wilhelmus Jan Hendrik Jeroen Meijerink was born on October 27, 1961 in Hoeven (Nbr.), The Netherlands. He attended secondary school at the 'Pius-X-college' in Almelo from 1974 to 1980. He studied medicine at the Catholic University Nijmegen, The Netherlands, and obtained his M.D. degree in March 1988. From March 1987 till October 1987 he worked as 'student doctor' in the Biharamulo District Hospital, Tanzania. From October 1987 to April 1988 he was research fellow at the University of Antwerpen at the laboratory of Prof.dr. R.H.G.G. van Hee. From April 1988 he was research fellow and member of the Nutritional Support team at the Academic Hospital Maastricht in the metabolic and nutrition research group of Prof.dr. P.B. Soeters. From January 1990 he is in training as surgical resident in the Academic Hospital Maastricht (Chairman Prof.dr. G. Kootstra).