ISSUES IN PROFESSIONAL PRACTICE

NUTRITION AND ENHANCED RECOVERY IN SURGERY

Highlights of a conference held on 11th and 12th January 2013 in Zurich, Switzerland

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FOREWORD

Issues in Professional Practice (IIPP) is a series of booklets published by the Association of Surgeons of Great Britain and Ireland to offer guidance on a wide range of topics which impact on the daily professional lives of surgeons. Some booklets focus on clinical issues, some cover management and service delivery, whilst others feature broader aspects of surgical working life, such as education, leadership and the law.

This latest IIPP booklet on Nutrition and Enhanced Recovery in Surgery represents the proceedings of a two-day international meeting held in Zurich in January 2013. The meeting was hosted by Nestlé Health Science in partnership with ASGBI. The speakers, all of whom were internationally recognised experts, were asked to provide an overview of their topic, based on a review of world literature, and then make recommendations for clinical practice.

There was unanimous agreement that nutrition is an important component of enhanced recovery, and that all patients should undergo nutritional screening before major surgery. There is increasing support for the use of immunonutrients, both before and after surgery, recognition that the gut should be used whenever possible, and also ongoing debate about the optimal method of providing enteral nutrition.

This booklet provides a series of brief summaries of each presentation given in Zurich. The topics cover many different aspects of nutrition and enhanced recovery and will, I am sure, be of interest to anyone involved in the care of patients undergoing major abdominal surgery.

The Association has published this booklet and others in the series to provide concise advice and guidance on current issues in surgery. The IIPP series provides a helpful and accessible resource to support your professional practice and all publications are accessible online at www.asgbi.org.uk/publications.

Suggestions for any potential topics for future booklets in the Issues in Professional Practice series would be welcome.

Professor John Primrose
President

president@asgbi.org.uk
INTRODUCTION

The objective of the two-day meeting was to share experience about the role of nutrition in, and around, surgery, with a particular focus on the field of post-operative outcomes and enhanced recovery. The meeting provided up-to-date approaches on nutrition as part of enhanced recovery programmes, a state-of-the-art review of current knowledge regarding surgical nutrition practice, and a discussion on the implementation of clinical guidelines in routine practice.

Conference Chairs and Scientific Committee

Christophe Mariette
Professor of Surgery, University Hospital C Huriez, Lille, France

Riccardo Rosati
Professor of Surgery, University of Milan, Italy

Dileep Lobo
Professor of Gastrointestinal Surgery, University of Nottingham Digestive Diseases Centre, Nottingham, UK

The meeting was accredited by the Association of Surgeons of Great Britain and Ireland and sponsored by Nestlé Health Science.
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POST-OPERATIVE OUTCOMES

EuSOS Study (European Surgical Outcomes Study)

Rupert Pearse
Barts and The London School of Medicine and Dentistry
United Kingdom

It is estimated that there are 234 million major surgical procedures worldwide every year [1]. Although the true mortality rate is not known, a preventable death rate of 1% would result in 2.3 million avoidable deaths per year. Generally, the quality of surgical outcome data is poor, making it impossible for institutions to compare data and learn from best practice.

Pearse et al (2006) reported that a group of 10% to 15% high risk in-patients are responsible for about 80% of surgical deaths. If these patients could be identified more effectively, the mortality rate could be significantly reduced [2]. A National Surgical Quality Programme, carried out in the USA, found that the overall complication rate following surgery was fairly consistent across institutions, at around 25%, but that the mortality rate varied from 12% to 21% [3]. This suggests some institutions may manage complications better than others.

The driving force for the European Surgical Outcomes Study (EuSOS) was to improve understanding of the overall surgical population in Europe, stimulate further research and audit in this area and ultimately to reduce the number of preventable deaths. During the course of a single week in April 2011, the aim was to include every eligible adult surgical patient into the study, and to follow them up until hospital discharge. Patients undergoing day case surgery, neurosurgery, obstetrics, and cardiac surgery were excluded, as they have separate care pathways.

Anonymised data was collected via a web-site, along with information about each institution including its size, case mix, critical care facilities and so on. The information collected was intended to establish: hospital mortality rate; duration of stay; standard of care; whether standards differed across Europe; whether mortality differed across Europe; and the determinants of admission to critical care following surgery.

Within the region of geographical Europe, nearly 2,000 investigators from 498 hospitals in 28 countries took part. After 446 subjects were excluded, there were 46,539 patients available for analysis, or around 1% of global surgical activity during that week. The median hospital stay was three days (range: 1 to 7), and 3,599 patients (8%) were admitted to critical care either through an elective or emergency procedure, where the median stay was 1.2 days (0.9 to 3.6).

Overall, there were 1,855 deaths in hospital, a rate of 4%, but there was significant national variation in this figure. Of these patients, 1,358 (73%) died without being transferred to a critical care unit. There was wide international variation in the adjusted mortality risk, but the confidence intervals were very wide suggesting a greater potential for bias. However, the variation does suggest that there were likely to be preventable deaths occurring in some countries and that steps could be taken to improve outcomes. In a subsequent sensitivity analysis, hospitals that had enrolled small numbers of patients, and those at the limits of the 95% quintiles, were excluded. The overall mortality rate was reduced to 3% from 4% but this is still unacceptably high.
There was also wide variation in the use of critical care resources: the elective surgery critical care admission rate varied from 1.5% in Sweden to 11.4% in Spain. The definition of critical care across the region is not standard, but it does seem as if the allocation of post-surgical critical care was not always logical or appropriate.

In summary, the mortality rate after surgery across Europe is higher than anticipated, and international variation in mortality rates suggests that preventable deaths are occurring. It is possible that poor provision of critical care contributes to these deaths.

The study was funded by ESICM and ESA.

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**Nutrition and outcomes in surgery and oncology**

Jens Kondrup  
Rigshospitalet, University of Copenhagen  
Denmark

In 2008, a study followed 5,051 randomly selected adult patients admitted consecutively to 26 hospital departments around Europe and the Middle East, and concluded that nutritional status was an independent predictor of clinical outcome 10. The EuroOOPS study assessed patients at admission using the NRS (Nutritional Risk Screening) 2002 tool and found that those patients who were “at risk” had more complications, higher mortality and longer length of...
stay than “not at risk” patients, even when adjustment had been made for confounding factors. The rate of complications increased with increasing age, type of surgery, cancer and co-morbidities, but also independently with nutritional status. The EuroOOPS study team concluded that, for almost every complication, the primary disease determines the type of complication while the nutritional status affects the probability that it will occur [1].

A secondary analysis of the mortality following complications after surgery in the EuroOOPS study found that patients deemed not at risk had a mortality rate of 3.0% compared to 28.6% of those patients nutritionally at risk. Multivariate logistic regression analysis showed that the independent odds ratios for death were 13.1 for being at risk and 12.5 for having a complication, but were not increased by co-morbidities, cancer or age.

A meta-analysis of 27 RCTs which measured complications in 1,710 patients, and 30 RCTs which measured mortality in 3,250 patients, found that the rate of complications can be reduced from 46% to 28% through the use of nutritional supplements, either delivered orally or via tube feeding [2]. The impact was particularly striking for infections, which were reduced from 44% to 24%, while mortality was reduced from 24% to 17%. This analysis also identified a number of benefits of improved nutrition, ranging from effects on muscle and bone cells to patient-oriented outcomes.

Studies have reported a wide variety of clinical outcomes related to nutritional status, and it is difficult to identify one variable that can be applied to all types of patient [3].

A study by Starke et al (2011) illustrates the difficulty in powering studies to detect significant differences in outcomes. This study randomised 132 patients who were nutritionally at risk, to a routine of standard treatment or targeted individual nutrition care [4]. Those in the intervention group had higher energy intake, with more reaching their protein goals. They had fewer complications, reported a greater improvement in well-being, and a lower readmission rate within 6 months following discharge, confirming that nutritional support can reduce the rate of complications in a group of internal medicine patients. All differences between the groups were statistically significant, but the study was slightly under-powered: for example, the power for reduction in complications was below the usual requirement of 80%.

Two studies reported interesting findings regarding other factors that might be affected by poor nutrition. Keele et al (1997), in a study of 100 patients undergoing GI surgery, found a significant reduction in overall complications in those patients managed with nutritional supplements, relative to those on a normal ward diet [5]. Interestingly, muscle strength loss, as measured by handgrip strength was also significantly greater in patients without nutritional supplements. In a similar study on 101 patients, Beattie et al (2000) also compared two groups of patients undergoing surgery, one of which was managed with routine nutrition and the other with nutritional supplements [6]. Over a period of eight weeks, patients in the control group lost significantly more weight than the other group, and anthropometry, grip strength and quality of life were also significantly different from the group receiving nutritional supplements (p < 0.001). These two studies demonstrated that hand grip strength may be a more sensitive factor than other clinical outcomes in determining the effects of nutritional status.

These studies help us to plan trials to assess the effects of nutritional supplementation during and after surgery. The numbers of patients that
need to be recruited is linked to the chosen endpoint. To detect changes in organ function, we probably need two groups of 40 patients, while to detect differences in complication rates, length of stay, quality of life, cost and so on, we would probably need two groups of 200. If we believe that nutritional supplementation can improve cell function, then it might be worthwhile to turn our attention to one of the variables associated with organ function that can act as surrogate markers for other outcomes.

In conclusion, ideally we would study hard end points such as mortality or complication rate. However, in populations that have low rates of these endpoints, unfeasibly large studies of thousands of patients would be required to detect a difference. A pragmatic alternative in pilot studies is to use surrogate variables such as hand-grip strength, or the sit-to-stand test.

References:


Hot topic: post-operative parenteral nutrition

Greet van den Berghe
Catholic University of Leuven
Belgium

There is little doubt that under-feeding in ICU patients is associated with adverse outcomes and is correlated with an increased rate of complications, particularly infections [1]. However, causality cannot be established merely by association: it is possible that those patients who are at higher risk of dying are also the ones who cannot be fed. Or it could be those who are not fed adequately are at higher risk because of the under-nutrition.

The only way to establish causal association is to conduct an RCT with blinded treatment allocation, but such a study has not yet been carried out, and there is still no real evidence to support one approach over another. Reliance on enteral nutrition (EN) leads to a high risk of under-feeding, while a combination of EN plus parenteral nutrition (PN) increases the risk of over-feeding and metabolic disturbance.

However, this lack of hard evidence has not prevented experts from constructing guidelines that recommend approaches to feeding in ICU. ESPEN guidelines advocate PN within two days if EN is insufficient, while ASPEN recommend that there should be no PN until 7 to 10 days [2, 3]. The EPaNIC trial was set up in an attempt to resolve this conflict [4].

Two approaches, an early and a late PN feeding strategy, were randomly administered to 4,640 adult ICU patients at risk of malnutrition during the first week of admission. In both groups, EN was initiated on the day after admission and vitamins and minerals were administered early in both groups. Over-feeding was prevented and insulin was infused to achieve optimal blood glucose levels.

There was a small difference in the primary endpoint, discharge alive from the ICU, in favour of late PN (P = 0.007).

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**EPaNIC : primary endpoints**

There was no difference in ICU mortality, but most other endpoints favoured late PN. There were fewer infections, better liver function, and hospital stay was reduced by two days. In terms of functionality, there was little difference at discharge, but patients on the late PN regime were discharged earlier. These differences might seem small, but the cumulative health economic impact is significant. A saving of 1,110 Euros per patient translates into an overall saving between the groups of 2.3 million Euros.

How can these results be explained? At first sight, it may seem counterintuitive that early parenteral nutrition to supplement EN should delay recovery. A subsequent analysis attempted to assess whether the effects of early PN were due to the severity of the illness or to the dose of macronutrients [5]. The analysis revealed that there was no beneficial effect of early PN associated with any type or severity of illness (as measured by APACHE II scores). The lowest dose of macronutrients was always associated with the fastest recovery. The amount of proteins or amino acids in the supplements, rather than the amount of glucose, appeared to explain delayed recovery with early feeding.

Under-feeding of patients in ICU appears to be beneficial, leading to better recovery from cell damage and better clearance of engulfed bacteria. An explanation for this was suggested by Vanhorebeek et al (2011) who stated that autophagy is an important physiological mechanism which appears to be impaired in critically ill patients [6]. Fasting is one of the most potent activators of autophagy, while insulin and growth factors suppress autophagy. Vanhorebeek et al speculated that insufficient autophagy in prolonged critical illness may cause inadequate removal of damaged proteins and mitochondria, which could explain lack of recovery in prolonged critically ill patients [6].

![Macronutrients suppress autophagy in muscle](image)

It has been shown that macronutrients also suppress autophagy in muscle. In an animal model, Derde et al (2012) confirmed by a randomised controlled study that quality of muscle was most disturbed in a group of critically ill rabbits that were fed with parenteral nutrition enriched with lipids or with amino acids, compared to those who were fasted or received predominantly glucose based parenteral nutrition [7].
In conclusion, under-feeding is prevalent among ICU patients and has been associated with adverse outcomes, but there is no hard evidence, only observational data, to support the addition of artificial feeding. The EPaNIC randomised controlled study demonstrated that postponing PN to beyond day eight in ICU patients at risk of malnutrition was superior to the prevention of caloric deficit with early PN.

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Am J Respir Crit Care Med (2012); November 29:Epub ahead of print

Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients
J Clin Endocrinol Metab (2011);96:E633-45

Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits
Endocrinology (2012);153:2267-76
ENHANCED RECOVERY IN ELECTIVE SURGERY

Enhanced recovery at national level: United Kingdom

John MacFie
Scarborough General Hospital
United Kingdom

Kehlet and colleagues from Denmark popularised the concept of “fast track” surgery in the 1990s. They suggested that a combination of epidurals, early mobilisation and early oral diet would facilitate the early discharge of patients [1]. However, these initial claims were based on observational data with selected patients.

The first randomised trial investigating “multimodal” surgical care was published from my unit in 2003. In this trial, a number of interventions before, during and after surgery were implemented which, taken together, contributed to improved physical and psychological function in the early post-operative period leading to earlier hospital discharge [2].

There is now little doubt that multimodal optimisation of care, or Enhanced Recovery Programmes (also known as ERAS, or enhanced recovery after surgery) as it is now called, is safe, and overall is superior to conventional care. However, doubt persists as to the mechanism of action of these Enhanced Recovery pathways. It is most likely that cumulative benefits occur as a result of marginal gains from each intervention.

Another important factor in the success of Enhanced Recovery Programmes is, in our view, the preservation and enhancement of gut function. Many factors in an Enhanced Recovery Programme impact on gut function: these include the avoidance of nasogastric (NG) tubes, fluid overload and early feeding. Most important, however, is probably the avoidance of opiates. The significance of gut function is not surprising when one considers that the gastrointestinal tract has a myriad of functions in addition to digestion. It provides a barrier function, it is the largest producer of cytokines in the body, it carries out antigenic sampling, and it maintains a stable ecoflora.

It is paradoxical, then, that gut function is not more widely recognised and used as a prognostic indicator, while inadequate gut function (IGF) often goes untreated in daily practice. One reason may be that IGF is difficult to measure, there is no quantifiable definition of IGF and assessment tends to rely on subjective measures such as bowel sounds, passage of flatus and passage of faeces. Given the importance of the gut, it is also strange that scoring systems such as the APACHE II score (Acute Physiology and Chronic Evaluation II) and the SOFA score (Sequential Organ Failure Assessment) do not include an assessment of gut function.

In an attempt to remedy this we carried out a retrospective audit in our institution and arrived at a working definition of IGF which was: an inability to tolerate 80% of calorific requirements over a period of 48 hours. This definition was subsequently applied to 315 consecutive patients entering our institution between May 2004 and May 2006. Information on nutritional parameters and requirements on entry were collected along with demographic and other data while outcomes such as complications, organ
failure and so on were recorded. The primary outcome was mortality at 6 months, which was found to be significantly affected by gut function (see Figure below). We concluded that gut function was, indeed, an independent indicator of prognosis in these patients [3].

Another factor which preserves gut function is the adoption of minimally invasive surgery. Minimally invasive surgery is not simply adoption of the laparoscopic approach; it also involves the avoidance of NG tubes and drains, bowel preparation, opiates, indwelling lines and the use, where possible, of small transverse incisions.

It is also important to reconsider the use of epidurals and spinal anaesthesia and to question whether they are fit for purpose. Epidurals can take a long time to be effective, are time-consuming, sometimes ineffective and potentially dangerous. They predispose to fluid overload and may reduce splanchnic flow. Alternative mechanisms such as the “painbuster” are safer, cheaper and effective.

In conclusion, the aim of enhanced recovery is to improve safety and quality and is not solely designed to bring about early discharge. Enhanced Recovery Programmes are evolving all the time as knowledge increases about recovery from surgical procedures. Enhanced Recovery Programmes are a process that involves the whole team, and they are made significantly easier with the support of a dedicated nurse.

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Fast-track surgery
Br J Surg (2005);92:3-4

Randomised clinical trial of multimodal optimisation and standard peri-operative surgical care
Br J Surg (2003);90:1497-504

Gut function in surgical patients
University of Hull; (2007)
Enhanced recovery in Upper GI: Unit experience

Shaun Preston
Royal Surrey County Hospital, Guildford
United Kingdom

The concept of any Enhanced Recovery Programme (ERP) is to improve outcomes through the promotion of multi-disciplinary team working to deliver protocol driven optimised peri-operative care. The recent literature is heavily influenced by colorectal surgery, but the principles are now being applied to a wide range of disciplines. There is very little literature on the role of ERPs in oesophageal cancer surgery. There is, however, literature on the use of standardised clinical pathways (SCPs), to achieve the same aims, which pre-date all publications on ERPs. Developed in the 1980s, SCPs are multidisciplinary management tools for specific clinical situations where tasks are defined, optimised and sequenced and the outcomes evaluated relative to the interventions.

SCPs were utilised in the management of major thoracic cases, including oesophagectomy, as long ago as 1994 [1]. Zehr et al developed and implemented a care pathway that significantly reduced cost and length of stay for patients who had undergone oesophagectomy, with a trend towards a reduction in mortality. Similar results were found when a “computerised clinical care pathway” was applied to a single series of 90 patients undergoing oesophagogastrectomy in Birmingham, Alabama [2]. The pathway was implemented upon admission, with the aim of streamlining care and reducing hospital stay while maintaining safety and patient satisfaction. The algorithm included such factors as ambulation, tube feeding, use of NG tube and epidural analgesia. When implemented, it resulted in a median length of stay of 7 days, a mortality rate of 4.4%, and a median ICU stay of 1 day. There was high satisfaction amongst the patients, but it was more difficult to implement in patients 70 years of age or above. As a result of these interventions, 30 day mortality in this population has dropped from a level of around 33% in the 1950s to less than 5% today. Low et al (2007) applied an SCP to the peri-operative period in 340 consecutive oesophagectomies commencing in May 1999, and were able to achieve a very low mortality rate of 0.3%, and a mean hospital length of stay of 11.5 days (the median was estimated at approximately 8 days) [3].

Two more recent publications paint a similar picture. From China, Jiang et al (2009) report a median discharge on day 7, a 4% readmission rate and 2.3% mortality, following implementation of a fast track clinical pathway in 114 oesophagogastrectomy patients [4]. In Spain, Munitiz et al (2010) compared outcomes before and after the introduction of a written clinical pathway for patients undergoing transthoracic oesophagectomy [5]. They concluded that use of the clinical pathway significantly reduced pulmonary complications, post-operative mortality and hospital stay.

In our tertiary oesophagogastric referral unit, we had tried for five years, without a great deal of success, to mobilise our patients early following radical oesophagogastrectomy. We therefore observed the pathway developed in Seattle first hand. A multi-disciplinary team from our unit visited Virginia Mason Medical Center, Seattle, observed the SCP in action and then applied the principles successfully to our own practice.
Using the principles of the Standardised Oesophagectomy Clinical Pathway (SOCP) we found that we could significantly increase the number of oesophagectomy patients being extubated in the immediate post-operative period. The number who were mobilised on the first day also increased markedly. We observed a reduction in complications, and in length of hospital stay (reduction of 6 days). ICU stay was also reduced, although the difference at this early stage was not significant [6].

The number of patients who have been through our pathway is still relatively low, but already we have been able to see a reduction in complication rate and length of stay in critical care, and an earlier discharge for patients who have been actively ‘driven’ through the pathway. The effects are not solely limited to patients being prepared and encouraged through the pathway. The principles of the pathway influence the management of other patients within the Unit and their immediate vicinity. Similar, but less marked, reductions in morbidity and length of hospital stay were also seen in patients whose management was not scheduled to rigidly adhere to the pathway.

To summarise: a standardised peri-operative pathway is able to facilitate delivery of the Enhanced Recovery Programme principles in patients undergoing major oesophageal surgery. These pathways are transportable, and can be adapted to different health care systems to produce a rapid change in outcomes. A key factor in adapting pathways developed elsewhere is that they have to be applicable to the existing procedure, practice and facility. Education and communication with the patient, their family and the extended hospital team is critical to successful implementation.

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Fast tracking after Ivor Lewis esophagogastrectomy
Chest (2004);126:1187-94
Strong for Surgery: Changing clinician and system behaviour to optimise surgical nutrition

David Flum
University of Washington
Seattle, USA

The Surgical Care and Outcomes Programme (SCOAP) was introduced in Washington State in response to a disturbing variation in outcomes reported by institutions in the region. In the period 2000 to 2003, the re-operation rate following elective colorectal resection was 17.7%, with a variation of plus or minus 38.2%. Many of the participating hospitals, therefore, had a complication rate well above 50%. Prior to the introduction of SCOAP, there was no mechanism in place for hospitals to compare their rates with other units and to understand what constituted best practice.

The SCOAP programme is entirely voluntary, and 60 units across the state were signed up one at a time. All agreed to do prospective audits and quarterly benchmarking. Some of the parameters that are measured are albumin levels, antibiotic use, pain control and GI function, while a surgical checklist encourages processes such as leak testing.

Over the period 2006 to 2009, the rate of significant complications in participating institutions had dropped to 9.6%, and the variability had dropped 10 points to ±29.4%. An improvement was also seen in leak testing following surgery; from 2005 to 2011 the percentage of units carrying out regular leak testing grew from 45% to 80%.

As well as improving the quality of healthcare for thousands of patients, these changes also bring about cost savings. The introduction of SCOAP has had a significant effect on costs through the avoidance of complications (see Figure below).

As the quality of the surgery has improved, attention has turned to decisions that are made pre-operatively, particularly those regarding the nutritional status of the patient. Optimisation of nutritional status occurs long before the patient enters the operating theatre, therefore attention needs to be shifted to the doctor’s office or clinic. We have launched a campaign called “Strong for Surgery” which is a public health campaign focusing on optimisation of nutritional status, blood sugar control, medication control and smoking cessation in preparation for surgery.
The evidence for optimisation of nutrition is overwhelming, but there is a large knowledge gap. Many physicians believe nutritional assessment is cumbersome, that intervention delays surgery, that the benefits are modest and that supplements should only be used for malnourished patients. The reality is that assessment takes no more than 5 minutes, with no delay to surgery, and there will be major benefits in 40% to 50% of patients, not just those who are malnourished.

In a meta-analysis of 26 RCTs investigating the effects of immunonutrition, 2,496 patients undergoing major open GI surgery received either immunonutrition (n = 1,252) or standard diets (n = 1,244). Patients in the intervention groups experienced a reduction in infection rates of around 46% and a reduced length of stay of about 2 days.

Universal screening for malnutrition now takes place with the assistance of a simple checklist of only six questions that can be used to identify quickly those patients at particular risk, (see Figure below).

![Bending the Cost Curve](image_url)

**Nutrition Screening Checklist – All Patient**

- **Screening for Malnutrition**
  - Is BMI less than 20?  
  - Has the patient had unexplained weight loss of more than 5% in the last 3 months?  
  - Does the patient have a poor appetite – eating less than half of meals or fewer than two meals per day?  
  - Is the patient unable to eat or feed orally due to dysphagia, weakness, or diarrhea?

- **Lab Tests for Risk Stratification**
  - Is the patient having major surgery?

- **Screening for Use of Supplements**
  - Is the patient having complex GI surgery (example: GI anastomosis)?

**Note:** EWS form.
There are many reasons why physicians don’t follow guidelines, even when they believe them to be of value [2]. To bring about change in the behaviour of a whole community, SCOAP partnered with a University of Washington led research network called CERTAIN (comparative effectiveness research translational network). CERTAIN has been building Washington State’s “learning healthcare system”, a network of healthcare organisations that participate in research projects, continuous evaluation of healthcare delivery and the achievement of better patient care. CERTAIN’s knowledge translation programme “Strong for Surgery” works with doctors’ offices and patients directly to optimise outcomes through the use of pre-hospital checklists and standardisation activities. “Strong for Surgery” incorporates evidence generated in CERTAIN projects back into the SCOAP hospital network and the CERTAIN clinic network. The programme also partners with national organisations such as the American College of Surgeons to target practice change through education and interventions.

In its development “Strong for Surgery” performed “deep dive” interventions at pilot sites which were helpful in understanding barriers and opportunities to make system changes without disrupting clinical practice. The pilot data suggested that the greatest barriers to offering pre-operative nutritional screening and support included confusion about indications, payment and access to product, and this led to the development of tools, resources and educational materials for staff and patients. “Strong for Surgery” was modified to account for these barriers, and the programme is now widely deployed, with the aim of 100% use by surgeons who are performing gastrointestinal anastomoses.

As the “Strong for Surgery” initiative adds new sites and clinical specialities, we continue to track outcomes and process of care related to nutrition in the SCOAP programme. “Strong for Surgery” is a public health campaign broadly applicable to all healthcare settings and is an exciting example of knowledge transfer related to nutritional support.

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TRENDS IN SURGICAL ONCOLOGY

Role of neoadjuvant therapy

Martin Fey
Inselspital Hôpital de L’Ile, Bern
Switzerland

The literature on the role of neoadjuvant therapy in gastric cancer is confusing and contradictory, and it is difficult to draw firm conclusions about treatment strategies. We surveyed the literature on the role of multimodal therapy in the treatment of oesophageal cancer, and want to draw attention to some of the pitfalls awaiting the unwary.

The first RCT to investigate surgery alone versus combined therapy in the treatment of oesophageal adenocarcinoma, suggested that the combined treatment led to significantly better survival \[1\]. However, a second look at the surgical results suggested that these were far lower than those found in other institutions; with the result that the multimodal treatment appeared to be artificially high by comparison. It was also suggested that the most important factor in this study might have been intense surveillance of the multimodal patients rather than any specific aspect of the treatment.

A trial published just two years later found no difference in survival between patients with localised oesophageal cancer treated with surgery alone or those treated with chemotherapy in addition to surgery \[2\]. However, the chemotherapy group did not receive radiotherapy, suggesting that this treatment might be an important factor in survival.

A paper in 2009 \[3\] compared two groups of patients with adenocarcinoma of the oesophago-gastric junction. Both were treated with chemotherapy and surgery, but one group also received additional chemo-radiotherapy. There was a trend towards better survival in the latter group, but the study was closed early before statistical significance could be achieved.

A meta-analysis published in 2011 \[4\] of 13 trials found that chemotherapy plus surgery was better than surgery alone. Twelve out of the 13 studies favoured the combined treatment, and national and regional guidelines now support this view, providing that the patients are judged to be operable.

Histological analysis of tumours shows that pre-operative radio-chemotherapy can eradicate tumour cells, resulting in histopathologically proven complete remission. The question arises, therefore, as to whether surgery is really a necessary part of the treatment of oesophageal cancer, or whether in selected cases combined treatment on its own can be just as effective.

Again, the answer is not clear-cut. A 2012 review assessed RCTs in the treatment of oesophageal cancer which compared results from definitive chemo-radiotherapy without surgery, with either surgery alone or surgery with induction chemotherapy or chemo-radiotherapy. In terms of overall survival, neither treatment showed any benefit over the other. On the other hand, surgery was of benefit in limiting local progression, while chemo-radiotherapy was superior in limiting spread of metastases \[5\].

Given that overall survival was similar with both treatment modalities, is it sensible to begin treatment with surgery before administering adjuvant treatment, thus avoiding the problems and toxicities with chemotherapy
and radiotherapy? While there may be a logic to this treatment strategy, a 2001 study of patients with adenocarcinoma of the stomach or gastro-oesophageal junction, found that nearly one-third of patients did not complete post-operative adjuvant chemotherapy, with toxic effects and patient refusal being the two major reasons for discontinuation [6]. Therefore, although the evidence points to this being a sensible approach, patient factors and feasibility limit its effectiveness.

This may change with the development of new drugs which are more highly targeted than traditional chemotherapy. Drugs targeting the Epidermal Growth Factor Receptors (EGFR) on carcinoma cell membranes halt an intracellular signalling cascade that stimulates proliferation and growth. These have shown promise in oesophageal as well as other cancers. For example, overall survival in colon cancer patients with a wild-type status of the K-ras gene, was significantly improved when cetuximab was added to best supportive care [7].

In conclusion, surgery alone for oesophageal cancer is no longer deemed to be an adequate treatment option. Chemo-radiotherapy given preoperatively is increasingly seen to be the best strategy to improve survival, to control local progression and to limit the development of distant metastases.

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Health related QoL in oncology and surgery

Franck Bonnetain
CHU Besançon
France

When clinical trials in oncology are being carried out, it is essential to choose a primary endpoint which is of clinical benefit to the patient.
Clinical endpoints include survival, health-related quality of life, fatigue and pain. Biomarkers, which are directly related to biological or pathogenic processes or pharmacological responses, can also be used once they have been validated as surrogates of a clinical endpoint \textsuperscript{1,2}.

In their guidance for industry, the FDA makes it clear that they will accept quality of life (QoL) or other relevant patient-reported outcome measures as clinical endpoints for regulatory approval. There has been much discussion about QoL in this context, with general agreement that true clinical benefit depends on whether the patient has improvement in the quality or quantity of survival. There needs to be clarity in the reporting of benefit associated with anti-cancer therapies so that survival is not achieved at the expense of quality of life.

Looking ahead to future trials, an EORTC workshop on clinical trial methodology in the older cancer patient proposed that QoL measures should be incorporated as co-primary endpoints in future trials \textsuperscript{3} and in neoadjuvant T3-T4 rectal cancer with pCR or local control to deal with bending limitation of early results \textsuperscript{4}. However, there are difficulties: is the endpoint technically sound (reproducible, valid etc), can a causal linkage between the intervention and the outcome be supported by evidence, and can the findings be translated into information that will be acceptable to decision makers \textsuperscript{5}? Moreover, can the measures be used not only in clinical trials, but also in routine practice?

The World Health Organisation definition of “health” is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity. Health-related QoL definitions must, therefore, include at least these dimensions and constitute measures of perceived health by the patients. Therefore, health-related QoL is composed of symptom status, functional status, general health perception and overall QoL which reflect the characteristics of the patient and the social environment (see Figure below) \textsuperscript{6}.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{health-related-quality-of-life-model.png}
\caption{A causal pathway model of health-related quality of life. The horizontal arrows indicate the main, but not exclusive, direction of causality. Wilson IB, Cleary PD. JAMA 1995;273:59-65}
\end{figure}
Gotay et al (1992) suggest that QoL should be measured where it is the primary endpoint, in non-inferiority trials, when treatment is expected to have no impact on overall survival (OS), or where there may be improvement of OS but also increased toxicity [7]. Moinpour et al (1989) suggested its use in trials of adjuvant therapy, advanced cancer or palliative care, and trials comparing different therapeutic strategies, such as surgery alone or chemoradiotherapy [8]. Today, QoL is seen as an essential co-primary endpoint along with tumour outcome to ensure impact of treatment in terms of patient clinical benefit.

In selecting a QoL tool, self-evaluation by the patient is always the best method, but may not always be possible. A tool is needed which is reproducible, and valid with respect to content, and ideally with the target population. Generic tools can be used to compare the QoL of different populations while customised tools are preferable for the investigation of specific pathologies.

The problem of missing data is very common in QoL studies and can lead to loss of statistical power, and can also increase the potential for biased estimates. It is important to understand the reason for data being missed. Is it simply random lack of data due to missed assessments or drop-outs, or is the lack of data linked to QoL issues? Different statistical strategies are required to deal with these situations.

A breast cancer study comparing the QoL of patients following sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) illustrated the longitudinal analyses of QoL measures using dedicated statistical tools dealing with missing data: SLNB improved the global health score and arm symptoms 12 months after surgery. However, SLNB combined with ALND resulted overall in a poorer QoL [9]. Hamidou et al (2011) also proposed an alternative approach for comparing longitudinal QoL using a time-to-event method or a time-to-QoL-score deterioration. Similar results were found, but with a statistical approach clinically meaningful for the clinician [10].

Increasingly, QoL is regarded as a major prognostic factor of overall survival in cancer. Individual studies have shown baseline QoL to be a prognostic indicator of survival, a finding that was confirmed in a meta-analysis which suggested that health-related QoL scales can provide prognostic information and predict survival in patients with cancer [11]. A recent work in hepatocellular carcinoma has demonstrated that QoL is the best parameter to add to prognostic score to improve assessment of OS, perhaps enabling treatment to be targeted to patient QoL [12].

In summary, quality of life is a major criterion in the assessment of clinical benefit in cancer trials, as the main tumour parameters are not necessarily valid surrogate markers of survival. QoL parameters should be the primary endpoint in studies where no benefit in outcomes is expected. In clinical practice, new interventional studies should be done to assess the added value of using QoL in clinical practice. QoL is a major prognostic indicator and can, therefore, be used to stratify or assess patients for inclusion in trials, as well as in clinical practise. Targeted treatment should be based on QoL profiles.

On-going research is necessary to improve the longitudinal statistical analysis of QoL, to optimise QoL follow up in order to detect clinically meaningful changes and to assess the impact of toxicities, recurrence and progression on QoL. There is no doubt that there are problems in using
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Quality of life in oncology and surgery

Jens Kondrup
Rigshospitalet, University of Copenhagen
Denmark

A systematic review of trials investigating oral nutritional supplements (ONS) in malnourished patients with cancer confirmed that ONS are effective at increasing nutritional intake and improving some aspects of quality of life (QoL), but they did not appear to improve survival or reduce complications.¹¹
Similarly, a 2011 study, among patients at risk of malnutrition in a department of general internal medicine, randomised to standard treatment (n = 66) or individual nutritional care (n = 66) showed that nutritional intervention led to fewer complications (p = 0.035), lower use of antibiotic therapies (p = 0.03) and fewer readmissions (p = 0.027). It also led to an improvement in the physical summary component of SF-36 [2].

A similar study randomised 80 malnourished GI patients, following discharge from hospital, to a three-month intervention of high protein and energy supplements or nutritional counselling [3]. Body weight and body cell mass improved significantly in both groups, but handgrip strength improved only in the ONS patients. ONS patients also experienced significantly fewer readmissions. The change in handgrip strength corresponded with changes in physical functioning, as evaluated by SF-36. All eight scales of the QoL assessment improved in the ONS patients, compared with only three in the dietary counselling group.

The QoL scoring system, SF-36, has been modified for use as a utility score: SF-6D. In 2002, Brazier et al attempted to quantify the health benefits associated with improvements in QoL experienced by patients as a result of various interventions. Using a group of 611 volunteers, Brazier et al were able to generate a hierarchy of QoL aspects that were most preferred by the volunteer regarding physical functioning, physical and emotional role, social functioning, bodily pain, general health, vitality and mental health [4]. The aim was to produce a utility measure that would quantify health benefits relative to the cost of treatment, assessed in terms of the price that a person is willing to pay to gain QALYs (quality adjusted life years).

Applying these measures to the patients in their 2008 intervention study, Norman et al (2011) were able to assess the cost of the post-hospital supplementation with ONS relative to the improvement in QoL experienced by these patients [5]. The group receiving oral supplements improved twice as much as the control group, but the intervention was...
associated with significantly higher costs, of 12,099 Euros per QALY. However, this was deemed to be cost-effective according to international thresholds, which require that new treatments should improve QoL for no more than 50,000 Euros per QALY.

The SF-36 QoL tool records subjective parameters, and it would be useful to develop objective measurements that agree with the subjective parameters. For instance, timed “up-and-go” tests and handgrip strength can measure mobility, while mental functioning can be assessed using Addenbrooke’s Cognitive Examination (ACE) and Continuous Reaction Time (CRT). However, these measures need to be validated before being used routinely as supplementary measures of QoL.

Jakobsen et al (2010) confirmed that handgrip strength was directly related to some SF-36 components and could be a valid measurement of mobility and QoL in patients. In 2011, the same group investigated the validity of CRT as a simple bedside tool for measuring cognitive function, and confirmed that simple reaction time tests were related to cognitive function and could be used to reflect cognitive function. However, CRT was not related to the mental component of SF-36. This component is mainly affected by mood, social drive and so on, rather than cognitive function, and is, therefore, not related to reaction time.

To summarise, quality of life measures may be sensitive to nutritional supplementation in patients where hard end points, such as death or complications, are not. Measurements of QoL allow cost utility calculations to be made to assess whether the intervention is desirable and cost-effective, but QoL recording should be supported with validated objective measures.

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Nutrition during neoadjuvant therapy

Christophe Mariette
University Hospital of Lille
France

Despite the poor prognosis when used alone for locally advanced tumours, surgery remains the standard treatment for upper GI cancer. The addition of radiotherapy and/or chemotherapy has also been investigated in attempts to improve survival. Due to local effects of the tumour, patients with upper GI cancers are at high risk of malnutrition, with around 80% of patients already experiencing some degree of weight loss by the time of diagnosis [1, 2].

Side effects of treatment can also lead to reduced food intake. Following surgery, protein, calorie, vitamin and mineral requirements are higher, patients are more at risk of infection, and wound healing is compromised [3]. Toxicities due to chemotherapy also impact on nutritional status resulting in appetite loss and nausea. Approaches are needed in order to relieve associated pain and minimise toxicity.

Recent clinical evidence supports the role of enteral nutrition (EN) in cancer patients through maintenance of quality of life (QoL), reduction in related morbidity and mortality, reduction in length of stay, enhancement of dietary intake during radiotherapy and prevention of weight loss [4 - 7]. During chemotherapy, malnutrition is a risk factor for more frequent and severe dose-related toxicities, the need for more treatment breaks, diminished response, increased risk of post-operative complications, impaired QoL, fatigue, reduced performance status and muscle function [8 - 12]. But would nutritional support actually improve post-operative outcome?
A meta-analysis from 1994 analysed seven trials and concluded there was no benefit for survival, tumour response, or chemotherapy-related toxicities [13]. However, the trial designs had serious shortcomings, small sample sizes, and used different compositions of EN, timing and duration.

A more recent RCT, involving 82 patients undergoing palliative chemotherapy for metastatic colonic cancer, investigated the role of parenteral nutrition (PN) versus no PN during the chemotherapy phase of treatment. In the PN group, the additional nutrition was found to slow weight loss, stabilise body composition, improve QoL, and reduce chemotherapy related toxicities [14].

Another recent RCT investigated the role of enteral nutrition in 91 patients undergoing neoadjuvant chemotherapy for oesophageal cancer. Patients were randomly assigned to EN or PN. Total and dietary intakes were equal in both groups, and there was no difference in serum albumin or body weight change. However, chemotherapy related toxicities decreased in the EN group with leukopaenia grade 3 of 17% vs 41% (ns) and neutropaenia grade 3 incidence of 36% vs 66% (p = 0.005) [15].

A newly published trial compared outcomes in 28 oesophageal cancer (OC) patients given intense nutritional support (INS) with those of 37 OC patients treated before the INS strategy was implemented. The effects of INS were tested at various stages, including before chemotherapy, and after surgery. The adjusted Odd Ratio for serious post-operative complications (0.23) was significantly lower in the INS arm and patients in this group preserved their pre-operative weight [16].

We have found that it is also best to implement supplementary feeding early in the treatment process of patients with oesophageal cancer or gastric cancer. Even in relatively well-nourished patients, oral supplementation can be of benefit [17].

What is the role of omega-3 fatty acids during neoadjuvant chemotherapy? Animal studies have shown that they can reduce chemotherapy related toxicities, including intestinal damage [18, 19]. In humans with lung cancer, fish oil was found to prevent deterioration of weight and muscle mass during chemotherapy [20].

Based on these findings, we have designed a double-blind phase III RCT to investigate the relation of immunonutrition to quality of life in patients with upper GI cancer, undergoing neoadjuvant treatment prior to surgery [NCT01423799]. Our hypothesis is that the immunologically active components in nutritional support may improve tolerance to anti-neoplastic therapy with an effect on overall outcomes and QoL. The primary objective is to assess health related QoL 30 days after surgery, and there are a number of secondary objectives such as tumour response and effects on post-operative infections.

In conclusion, in upper GI cancer, malnutrition increases the risk for post-operative complications, the side effects of neoadjuvant treatment and surgery, toxicity, the number of treatment breaks and decreases QoL and the responsiveness to chemotherapy. Further investigation is needed into the role of nutritional support during treatment which may preserve weight, reduce toxicity and post-operative complications.
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EARLY MOBILISATION AND MINIMAL ACCESS SURGERY

The role of early mobilisation in the immediate post-operative period

Donald Low
Virginia Mason Medical Center, Seattle
Washington, USA

Almost one in ten oesophagectomy patients dies following the operation. One meta-analysis of published data suggests that mortality could be related to the volume of resections carried out in an institution [1]. The difference in 30-day mortality rates between high and low volume institutions is significant: 0.73% compared to 2.09%, while in-hospital mortality is below 3% in high volume institutions compared to 8.5% in low volume.

However, mortality is not related solely to volume; there are a number of other factors including diversity of services, the existence of established pathways and databases, and the level of communication with oncologic nurse coordinators [2]. After carrying out 340 oesophagectomies using a dedicated clinical pathway, we achieved a combined in-hospital and 90-day mortality rate of less than 1%. Significant aspects of the care pathway are applied routinely to all patients: PCEA (patient controlled epidural analgesia), extubation in the operating room, jejunostomy, and early mobilisation.

Part of the standardised clinical pathway we use focuses on minimising blood loss. In 2003, we reported that intra-operative fluid restriction appeared to result in better outcomes [3]. Since then, our use of intra-operative fluid has reduced significantly, from 5 litres to 2.8 litres in 2010, with a similar reduction in blood loss.

Many surgeons have a problem with epidurals, believing them to be time-consuming and unreliable. However, in our view, epidurals help with early mobilisation, as well as leading to improvements in pain relief and recovery of GI function. There is certainly a defect rate of around 15%, but placement can be improved using the post-operative epidurogram. At VMMC, we have worked with our anaesthesiologists to increase their understanding of oesophagectomy and have developed “standard work” to be used intra- and post-operatively. There are some traditional approaches to post-operative care which need to be modified. Most patients were automatically ventilated overnight, but, since 1991, 98.5% of our patients have been extubated immediately following the operation. ICU staff need to be retrained to look at routinely mobilising patients following major cancer surgery.

In our current protocol, oesophagectomy patients are elevated to a sitting position 4 to 6 hours post-operatively, are walking in a corridor within 12 hours, and are taking six to eight walks of 220 feet per day by day 2. Independent mobility is expected by day 4. Currently, we are achieving mobilisation on day 1 in 92% of patients and in 72% on the day of surgery [4].

There are many practical aspects to achieving early mobilisation. In the ICU we have introduced Hill-Rom beds that tilt readily to put the patient in a sitting position. Chest tubes are connected to atriums that are easily moved, and patients are supplied with socks fitted with grippers to avoid falls.

All patients are fitted with a feeding jejunostomy before or during their operation and tube feeding starts the morning after surgery. Our low
mortality rates were not achieved in a selected population, similar outcomes were achieved with patients aged over 80 [5]. In a comparison of published in-hospital mortality rates in selected patients aged 80, our institution achieved a 0% mortality rate, which compares extremely well with previous studies. The conclusion is that physiology, not chronology, is the limiting factor in mortality in these patients.

Over the period from 1991 to 2011, median ICU stay dropped from 2 days to 1, median hospital length of stay dropped from 10 to 7 days, and 30- and 90-day in-hospital mortality dropped from 0.6% to zero.

An oncology nurse coordinator is at the centre of the standardised clinical pathway used at VMMC. Her role is to contact families before admission and make sure that patients and family know what to expect from enhanced recovery.

In summary, there are many elements that are important in the enhanced recovery process, including careful patient and family preparation, nutritional assessment and support, appropriate fluid management, immediate extubation and early mobilisation. The nurses involved must be empowered to design and, if necessary, modify the system and its pathways. It has recently been demonstrated that, under proper circumstances, these pathways can be transplanted to different hospitals and health systems [6].

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Minimally invasive surgery in oesophageal carcinoma

Riccardo Rosati
University of Milan
Italy

The role of surgery in oesophageal carcinoma is to remove disease, remove regional lymph nodes, and create a new alimentary conduit. It is not clear that this can always be done with a minimally invasive procedure, largely due to the need to clear lymph nodes.

There are three lymph node fields that need attention: field I in the upper abdomen where they are relatively easy to access; field II in the chest and field III in the neck [1]. Lymphadectomy in the third field is not routinely performed in western countries, where there is a preference for using chemo-radiotherapy instead: extensive thoracic and neck dissection can affect swallowing mechanisms which, in turn, affect recovery [2].

In the early 1980s, the role of laparoscopy in oesophageal cancer was solely diagnostic in order to exclude small liver metastases or focal peritoneal carcinomatosis. In a considerable number of patients, laparoscopy changed the subsequent therapeutic strategy, moving from surgery to neoadjuvant treatment or palliation, and avoiding unnecessary laparotomy. Since then, it has developed from simply being a part of the staging process to an integral part of the surgical procedure.

An increasing number of papers have reported on its use, often in combination with open surgery. Initially it was used in transmediastinal resection; then thoracoscopic oesophagectomy - combined initially with open abdomen and neck surgery. This was followed by total laparoscopic transhiatal resection [3] leading finally to hybrid minimally invasive oesophagectomy, which is now the most frequently carried out procedure [4]. Further modifications have taken place, such as thoracoscopic oesophagectomy and laparoscopic gastric mobilisations with cervical pull up [5] and radical extended abdominal, mediastinal and cervical lymphadenectomy [6].

Luketich et al described the original minimally invasive McKeown oesophagectomy procedure in 2003. Their experience of over 200 patients was reported, and included a reduction in post-operative pain and pulmonary complications [7]. They also reported a shorter hospital stay (7 days) and lower mortality rate (1.4%) than most open series reported at the time.

Later, in a review of over 1,000 cases of minimally invasive oesophagectomy, Luketich et al (2012) evaluated the outcomes of minimally invasive oesophagectomy comparing the modified McKeown approach (481 patients) with a modified Ivor Lewis approach (530). They concluded that minimally invasive oesophagectomies resulted in acceptable lymph node resection, post-operative outcomes and mortality with either approach, but the Ivor Lewis approach was associated with less recurrent laryngeal nerve injury [8].
An international survey of surgeons in 2009 found that minimally invasive procedures were now carried out in 14% of oesophagectomy cases, which compares with 30% in colorectal cancer [9]. This is reflected in the literature, with many new publications emerging in recent years and all reporting good operating times, reduced morbidity and mortality and excellent anastomotic integrity.

Our experience of oesophagectomy with gastroplasty for cancer now extends to almost 300 patients up to the end of 2012. Over half of these patients were operated on using a minimally invasive technique, mainly a hybrid procedure combining laparoscopy with open thoracotomy. In 184
patients, laparoscopic gastrolysis was carried out either as TTE (transsthoracic esophagectomy) with open thoracotomy; TTE plus VATS (video assisted thoracic surgery) plus left cervicotomy or THE (transhiatal esophagectomy) plus left cervicotomy. There was no significant difference in the three approaches, except that minimally invasive laparoscopy enabled a significant reduction in splenectomies, especially in patients with adenocarcinoma and high BMI. Historically these patients have always had a high incidence of splenectomy.

Whichever technique is used, there will be difficulties in removing the lymph nodes. It is important to identify the vagus nerve and preserve the recurrent laryngeal nerves (to avoid respiratory and swallowing dysfunction), the vena cava and other important vessels.

Following minimally invasive resection, there is no difference in overall survival but tumour grade and nodal status are highly associated with survival.

In summary, no single operation can be adapted to every patient; each patient needs their own approach. Although there seem to be advantages to minimally invasive procedures, the surgeon has to choose the right operation for each patient.

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In 2005, Fearon et al published the first systematic review on enhanced recovery following surgery, setting out an evidence-based consensus for clinical care of patients undergoing colonic resection [1]. The authors called for the use of a multimodal pathway to reduce surgical stress, reduce morbidity and aid recovery. A Cochrane review in 2011 of surgical recovery strategies found that Enhanced Recovery Programmes can reduce complications in colorectal surgery by 50% [2].

The Enhanced Recovery approach is made up of several components, each of which has an incremental effect on outcomes. It is difficult to identify which of the components is likely to have the most impact, but some, such as pre- and post-operative nutrition, pre-operative carbohydrate loading, adequate analgesia, fluids restriction and early mobilisation, are key elements, as observed in prospective studies.

Regarding the role of nutrition, Schiesser (2008), among others, pointed out a direct relationship between peri-operative malnutrition and post-operative complications [3]. In their study, 40% of malnourished patients suffered complications compared to 14% of adequately nourished patients. Major complications were also experienced more frequently by the malnourished group. The authors used the NRS (Nutritional Risk Score) 2002 to assess patients, and concluded that it was a very simple and reproducible assessment, with a good distinction between the various levels of risk and good correlation with risk for complications.

Despite these and other data on the role of nutrition in recovery after surgery, a survey about nutritional screening carried out in 77 hospitals in Switzerland and Austria revealed that selective nutritional support in hospitals is modest at best [4]. When asked how often nutritional screening was performed in patients scheduled for major surgery, fewer than 20% reported that they “always” performed a screening, 50% reported that they screen “sometimes” and 20% “rarely”. Ten per cent reported that they never do nutritional screening.
Of those who did carry out nutritional screening, 20% to 30% performed screening after surgery only, which is definitely too late to have any beneficial effect. Peri-operative nutrition is also not performed systematically, with 10% of respondents only doing it routinely, and 60% performing peri-operative screening “sometimes”. In around 85% of responses, the surgeon claimed responsibility for nutritional screening, while a multidisciplinary team was present in only 30% of institutions.

What is the evidence concerning immunomodulating components in the nutrition for surgical patients? Is it only the calorific component that is important, or do other factors such as arginine, omega-3 polyunsaturated long-chain fatty acids (PUFAs), RNA and anti-oxidants play a major role?

The evidence for immunonutrition has been assessed in two recent reviews: a systematic review in 2010 of high risk surgical patients [5], and one in 2011 of peri-operative arginine [6]. In addition, there have been two investigations into the cost-effectiveness of immunonutrition, one carried out in the USA and one in Switzerland [7, 8].

Marik et al (2010) reviewed data for 1,918 patients from 21 studies covering the period 1992 to 2008 [5]. Patients had undergone various elective surgeries including GI malignancy, head and neck malignancy, other GI surgery and cardiac surgery. Immunonutrition was found to significantly reduce the risk of acquired infections, wound complications and length of stay.

In the systematic review of peri-operative arginine, the results of 54 RCTs performed between 1995 and 2009 were assessed [6]. There was a positive effect associated with the administration of arginine, on infections, length of stay (LOS) and mortality.

An economic analysis conducted on the US national database, included 126 US hospitals with around 1 million patients [8]. A large decrease in LOS of 9.7 days was associated with the use of immunonutrition, along with a 51% decrease in risk of infectious complications. This translated into significant cost-savings particularly amongst medical patients, where the saving was over $2,000 per patient, even after including the additional cost of nutrition.

Similar results were reported in 2011 by Chevrou-Severac for a cost analysis in Swiss patients [7]. In 420 patients, they found a cost saving per patient of around 1,000 CHF if immunonutrition was given post-operatively, rising to over 2,500 CHF if immunonutrition was given pre-operatively. In a sensitivity analysis, they reported a strong correlation between cost savings and baseline infection rate.

Three meta-analyses in this area have also been recently published [9 - 11]. All three included around 20 studies, and reported a similar reduction in complications, infections and length of stay. Although three meta-analyses on the same topic are not absolutely necessary, the fact that they were performed reflects the great interest of the surgical community in this area.

Despite overall good results of immunonutrition, some studies in major surgery have reported negative results. The question is why? In an RCT involving 300 patients at nutritional risk, Huebner et al (2012) found little difference in clinical outcome, with no difference in complications between patients given immunonutrition and those given conventional nutrition [12]. Of note, this study enrolled a large number of severe cancer
patients, and tolerance of nutritional supplements was low. There may be a possible bias due to the fact that many patients did not take an adequate quantity of supplement. These results highlight the importance of patient compliance in the assessment of immunonutrition value in cancer surgery.

There are many reasons for poor compliance, and we are analysing our data to find out which are the most important. Information and education of patients, as well as support, are probably the key elements, along with the surgical team, including nursing staff to support the patient in this difficult peri-operative period.

In conclusion, nutrition should be considered as part of the enhanced general management of surgical patients. Good nutrition has been shown to reduce complications, and there is good evidence to support the use of immunonutrition.

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Immunonutrition: Evidence review in elective surgery

John Drover
Queen’s University, Ontario
Canada

Arginine is one of the most studied nutrients and appears to have a specific effect in surgical stress, which is different to that in critical illness. We carried out our systematic review of arginine supplemented diets on clinical outcomes in patients undergoing elective surgery, in an attempt to define the evidence that supports the use of arginine supplemented formulas in this group of patients.[1] We also wanted to understand how different administration strategies might affect outcomes.

The review was performed on studies carried out in the period from 1990 to March 2010. RCTs were included if they compared arginine supplemented diets with standard enteral feeds, in patients with scheduled procedures and where clinical outcomes were reported. We were looking primarily for reports of infectious complications, and secondarily for reports of hospital length of stay (HLOS) and mortality.

Sub-group analyses were carried out to assess a priori whether there were different outcomes in patients having GI surgery versus other types of surgery; upper versus lower GI surgery; arginine supplement + Fish Oil + nucleotides versus other types of feed and whether the time of administration had an effect.

Fifty-four published RCTs were identified, of which 35 were included in the analysis, once duplicates and trials with non-standard control groups or pseudo-randomisation had been excluded. Infection rates were reported in 28 studies, and overall a 41% reduction in infections was significantly associated with the use of immunonutrition (p < 0.0001). Two of the studies used glycine in control groups, but a sensitivity analysis showed that there was no change to the overall result if these studies were excluded.
The number of patients in many of these studies was relatively small, and statistical power was only achieved through combining the data. Overall, around 3,000 patients were included in the analysis. Some of the studies did not favour the use of arginine, and the confidence intervals of others extended across the centre point of the risk ratio analysis. However, this would be expected on a statistical basis, and the overall end result firmly favoured the use of arginine supplementation. There was no statistical heterogeneity.

Hospital length of stay was reported by 29 studies and, overall, the use of arginine supplementation was found to be associated with a median reduction in HLOS of 2.38 days. The result was not affected by the exclusion of studies where glycine was used in the control group. There was significant heterogeneity in these studies. Length of stay is notoriously variable as it is affected by factors such as cultural norms and health care systems which may account for the heterogeneity.

Mortality was around 2.6% in both groups: to see a difference in mortality in these patients undergoing upper GI surgery would require thousands of patients, far more than were available for this meta-analysis.

In the sub-group analysis, seven studies reported results of patients receiving pre-operative supplementation, which resulted in a 43% reduction in infections; 18 studies reported results for patients receiving post-operative immunonutrition, which showed a 22% reduction in infections due to supplementation. Thirteen studies reported peri-operative administration which was associated with a 54% reduction in infections. There is statistical evidence that administration before and after surgery may be optimal, but further studies would need to be done to confirm this hypothesis.

Patients receiving IMPACT appeared to benefit more than those receiving other products, some of which were not commercially available mixtures. Although it is difficult to find a pattern, the studies that did not use IMPACT generally delivered a lower dose of arginine and tended not to use omega-3 fatty acids.

To summarise, arginine supplemented diets in patients undergoing elective surgery are associated with a reduction in infections and hospital LOS. This is the case across different types of high risk surgery, although GI surgery has been the most studied. The most frequent dosing strategy is 750 to 1,000 ml given pre-operatively for 5 to 7 days, then immediately post-operatively via a tube, for 7 days, or until the patient begins eating normally. There is a large body of data on the use of arginine supplemented diets in this area, and the evidence for reduced infection is robust.

References:

Peri-operative fluid management

Dileep Lobo
University of Nottingham
United Kingdom

Fluids are the most frequently prescribed drug in hospital, yet many of those who prescribe them do not always understand their use. Maintenance
Fluid is the body’s normal daily requirement for water and electrolytes; replacement fluids are like-for-like replacement for on-going fluid loss in addition to maintenance; resuscitation fluids are required to correct an intravascular fluid deficit. Very often we find that a patient has been resuscitated successfully, but continues to receive resuscitation volumes instead of maintenance.

Fluids can be dangerous. In 1999, a significant number of patients were dying as result of infusion of too much or too little fluid by inexperienced staff. In a 2001 article, we reported that the responsibility for fluid prescription is often left to the most junior member of team, that there was wide variability in prescribing practice: about 26% of those who responded prescribed more than two litres of 0.9% saline per day, while about 50% prescribed potassium [1]. In 2005, Walsh et al reported that surgical house staff did not appear to be using the available fluid balance information, leading to about 17% of patients developing a morbidity directly related to the fluid they had been given [2].

The daily requirement for fluid for maintenance is only 2 litres per day, with 0.9 to 1.2 mmol/kg for sodium, and the same for potassium. Despite this, during and after surgery some patients will have received 8,000 ml of water, 1,200 mmol sodium, yet will have lost only 2,000 ml of liquid, and excreted 25 mmol sodium. Not surprisingly, these patients are in a state of fluid and electrolyte overload, leading to oedema which hinders recovery.

Large amounts of “abnormal” saline are used every year. The chloride concentration of this fluid is 1.5 times that of plasma. In animal experiments, the resultant hyperchloraemia has detrimental effects leading to chloride-dependent vasoconstriction in the tubules [3].

Chowdhury et al (2012) compared the physiological effects of Plasmalyte and abnormal saline in healthy volunteers using weight as a measure of fluid balance [4]. There were sustained high levels of chloride in the saline group, leading to a fall in strong ion difference, with these subjects becoming hyperchloraemic and acidotic. There was a significant reduction in mean renal artery flow velocity in the saline group, producing renal oedema (and, possibly, intra-renal tissue hypertension) and a decrease in renal cortical tissue perfusion.

One hypothesis for the mechanism is that the increased amount of chloride presented to the renal tubule leads to entry of chloride into the macula densa, depolarisation of the basolateral membrane, release of adenosine, vasoconstriction and ultimately reduction in renal blood flow and glomerular filtration rate.

Other evidence of the possible damage caused by excess chloride was provided by O’Malley et al (2005) [5]. In patients undergoing renal transplantation, there was evidence of harm in those patients receiving saline, compared to those receiving Ringer’s solution: creatinine clearance was diminished in this group, there was also a greater requirement for dialysis, and a greater incidence of hyperkalaemia and metabolic acidosis.

In 2012, Shaw et al reported the results of a review of patients undergoing major open abdominal surgery [6]. Patients received either saline (n = 2,778) or Plasmalyte (n = 926) during surgery. There were significantly fewer complications in the group receiving a balanced solution, compared to those
receiving saline: mortality was lower, and there were fewer major haemorrhages and infections. There was also a far greater use of resources, such as blood transfusion, blood gas analysis and dialysis in the saline group.

Yunos et al  (2012) reported the results of a longitudinal study comparing a change in fluid strategy for critically ill patients. In 2008, 760 patients received chloride-rich saline, while in 2009, 777 patients received chloride-restricted solutions. There was a significantly increased incidence of stage 2 or 3 acute kidney injury in the ICU in the saline group, and significantly more patients in this group requiring renal replacement therapy [7].

It is important to understand what is meant by “liberality” and “restriction” in clinical terms. In a large study, Brandstrup et al  (2003) investigated the effects of fluid restriction versus a standard regimen [8]. In a group of 141 patients undergoing colorectal surgery, the restricted group (n = 69) received sufficient fluid to maintain a constant body weight; while the standard group (n = 72) received pre-loading as well as regular infusion during and following surgery, according to standard practice. There was a significantly greater rate of complications in the standard group, and the complication rate was related to weight gain. Patients who received < 3.5 litres of fluid had a complication rate of around 25%, but this rose to over 60% in patients in the standard group who received more than 5 litres of fluid. A weight gain of > 2.5 kg increased the complication rate.

The critical question in fluid therapy is how much fluid is too much? The terminology of fluid loading has been imprecise and is the cause of some confusion, due to there being no standardised definition of “standard”, “restricted” or “liberal”. In a meta-analysis of nine RCTs reporting outcomes on peri-operative intravenous fluid therapy in 801 patients, Varadhan and Lobo (2010) found little difference in post-operative complication rates or hospital stay between “restricted” or other regimens. However, when the fluid regimens were reclassified according to whether
patients were in a state of fluid balance or imbalance, there was a significant reduction of 41% in complications and length of stay (3.5 days) in the balanced group [9].

Reporting the results of a review of flow monitors for fluid replacement in major abdominal surgery, Abbas and Hill (2008) advocate the use of flow guided intra-operative fluid therapy to provide continuous monitoring of cardiac output, enabling optimisation of intravascular volume and tissue perfusion. In a review of five trials recruiting 420 patients, they found there was a reduced complication rate, reduced length of stay, fewer ICU admissions, and an earlier return to bowel function with a flow-guided fluid strategy [10].

In conclusion, before we prescribe fluid to our patients, we need to ask two questions: does my patient need parenteral fluid? If yes, then for what reason? There are only three possible answers: to correct an intravascular deficit, to replace on-going losses, or for maintenance needs. The aim should always be to give the right amount of the right fluid at the right time.

References:
Nutrition and post-operative outcomes in colorectal cancer

Zeno Stanga
University Hospital, Bern
Switzerland

The ESPEN definition of malnutrition associates under-nutrition with changes in body composition and reduced function. However, it is important to add that malnutrition is also associated with poor surgical outcomes. One of the first studies to make this association was by Studely in 1936. He noted that, in patients undergoing surgery for chronic peptic ulcer, complications (including mortality) were much higher in those patients whose pre-operative weight loss was 20% or more.

In colorectal cancer patients, the incidence of malnutrition is often between 30% and 40%. DeWys et al (1980) reported that 54% of colorectal cancer patients have suffered measurable weight loss in the six months before surgery. The effect of weight loss on survival is to reduce it significantly from a median of 43 weeks to 21 weeks.

Following abdominal surgery, it was reported that well-nourished patients experienced significantly lower morbidity (29% compared to 72% of malnourished patients (p < 0.001)) and mortality, 4% versus 23% (p < 0.001). Later, Lieffers et al (2012), in a study of 234 colorectal cancer patients, demonstrated that low muscle mass can predict post-operative outcome. Patients with normal muscle mass had a length of stay of 10.6 days compared to 13.2 days in patients with low muscle mass. Patients with normal muscle mass also experienced a lower rate of complications, 12.6% compared to 23.1%. Low muscle mass was found to be an independent predictor for post-operative infection. The differences between the groups were even more pronounced in the elderly, where the complication rate in patients with normal muscle mass was 8.8%, compared to 29.6% in those with low muscle mass.
What should be the routine procedure for identification of nutritional risk? Patients should be screened 10 days before their operation, allowing time to provide nutritional supplements if required. Although there are many tools now available, including the Malnutrition Screening Tool (MST), the Malnutrition Universal Screening Tool, (MUST) and the Nutrition Risk Index (NRI), there is no expert consensus as to which is the best to use in cancer patients.

In Europe, the most commonly used tool is the NRS 2002 (Nutritional Risk Screening tool). Before the full screening, four simple questions are asked of the patient: BMI, weight loss in previous three months, reduced intake in last week, severity of illness. If there is a positive response to any one of the questions, the full screening has to be performed. The first part of the full screening assesses the degree of impaired nutritional status on a scale from 1 to 3. The second part requires an assessment of the severity of disease which is related to stress metabolism. The score for the two parts is added together, and an extra point is added if the patient is over 70. A final score of greater than 3 indicates severe nutritional risk or malnutrition, which would benefit from nutritional therapy.

Schwegler et al (2010) assessed the nutritional status of patients undergoing elective colorectal surgery, and established that the NRS 2002 tool was an accurate predictor of outcome. Complications were experienced by 62% of malnourished patients compared to 39.8% of patients not at risk (p = 0.004). Mortality was also higher in malnourished patients, but the difference was not significant, probably due to the small number of patients in the study.

Braga et al (2002) investigated the effect of nutritional supplementation on malnourished surgical cancer patients. Patients who were candidates for elective surgery for GI cancer, were randomised to receive post-operative enteral feeding with a standard diet within 12 hours of surgery (n = 50), another group received an oral liquid diet enriched with arginine
and other components for 7 days before surgery (n = 50) followed by standard feeding after surgery. A third group (n = 50) received enriched formula before and after surgery. Major complications, infectious complications, and length of stay (LOS) were all reduced in the intervention groups, but not all differences were statistically significant.

Later, the same authors carried out an economic evaluation of the study to assess the cost-effectiveness of nutritional intervention [11]. Despite the additional cost of nutrition, the cost of in-hospital routine care was similar in both groups.

Current recommendations from ESPEN are that if a patient is at severe risk, (more than 15% weight loss in 6 months, low BMI, Subjective Global Assessment grade C, low serum albumin low, and NRS 2002 score of 3+), they should be given oral supplements, enteral nutrition or parenteral nutrition, and ideally immunonutrition. Regardless of their nutritional status, patients should be given oral supplements before major abdominal surgery.

To summarise: pre-operative malnutrition is associated with increased post-operative morbidity and mortality. A nutritional screening tool such as the NRS 2002 is an easy and effective way to identify patients at risk. Fundamental peri-operative care should include correction of nutritional deficits before surgery, avoidance of pre-operative starvation and re-establishment of oral feeding as soon as possible. Pre-operative nutritional support is beneficial in malnutrition and pre-operative immunonutrition may reduce morbidity in major abdominal surgery.

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Early enteral nutrition following upper GI surgery: Jejunostomy or not?

Olga Tucker
University Hospital Birmingham
United Kingdom

Malnutrition is present in approximately 60% of patients with oesophageal cancer, and 85% of patients with gastric cancer. Malnutrition is associated with adverse clinical outcomes following surgery, including muscle wasting, increased morbidity including immune suppression and increased infection, increased risk of serious post-operative complications, delayed wound healing, prolonged length of hospital stay (LOS), pulmonary complications, leading to increased health care costs.

Options for nutrition after major GI surgery include nil by mouth (permissive short term starvation), total parenteral nutrition (TPN), nasojejunal (NJ) or nasoduodenal (ND) enteral feeding, percutaneous endoscopic gastrostomy (PEG), percutaneous endoscopic jejunostomy (PEJ), or feeding jejunostomy (FJ). The enteral route is preferred and is supported by major guidelines [1].

Several publications support early enteral nutrition. Fujita et al (2012) randomly assigned 154 patients to parenteral nutrition (PN) + NJ early enteral nutrition (EEN), or to partial PN following oesophagectomy. The overall rate of complications in both groups was similar, but the rate of life-threatening complications was lower in the EEN group, hospital LOS was shorter in the EEN group, and completion rate of the clinical pathway was greater in the EEN group [2].

Gabor et al (2005) treated 44 patients with EEN via double lumen NJ feeding or nasogastric decompression tube. TPN was commenced on post-operative day 1. Patients were assessed against a matched historical cohort of patients given PN. Oral feeding was initiated on post-operative day 7 in both groups. The EEN group had a faster return of bowel function, decreased infectious complications, decreased ICU and in-hospital stay, with no difference in mortality, cases of aspiration pneumonia or anastomotic dehiscence rate [3].

Farimani et al (2008) compared EEN with PN after resection of oesophageal cancer in 90 patients. EEN was started 8 hours post-operatively at 15 ml/hour with stepwise increases until total EN was achieved by day 6 [4]. Oral enteral feed was started in the PN group at post-operative day 7. There was no difference in infectious complications or overall 3 month mortality, but there was a shorter ICU and in-hospital stay in the EEN group.

Enteral feeding has a number of advantages over TPN. Enteral feeding provides the necessary micro- and macro-nutrients in a more intact form, it
maintains gut mucosal integrity, inhibits bacterial translocation, inhibits the cytokine response, reduces the secretion of stress hormones and has a decreased risk of complications \(^5,^6\).

The enteral route is preferred following major GI surgery, but there are uncertainties over the safest route and timing after oesophagectomy and gastrectomy. ESPEN guidelines recommend that normal food intake or EN be initiated early after GI surgery (Grade A evidence), and that oral intake should be adapted to individual tolerance and the type of surgery carried out (Grade C evidence) \(^1\). Placement of a needle catheter jejunostomy or NJ tube is recommended for all candidates for tube feeding undergoing major abdominal surgery (Grade A evidence). Post-operative tube feeding should be continued for 5 to 7 days after uncomplicated surgery (Grade C evidence). Tube feeding should be initiated within 24 hours of surgery and gradually increased which may take a period of 5 to 7 days to reach target intake (Grade C evidence).

There have been concerns about the timing of EN, in that gut motility is impaired post-operatively which may reduce its ability to absorb micronutrients. However, Sand et al (1997) reported that the small bowel recovers its ability to absorb nutrients almost immediately after surgery even in the absence of peristalsis \(^7\). In addition, EEN has been shown to preserve the integrity of the gut mucosa and maintain its immunological function \(^7\).

Feng (2012) reported on the impact of early EN on the intestinal motility of 35 patients following oesophagectomy. There was no delay in bowel function recovery or increase in GI symptoms compared to PN, although this was a small study \(^8\). Kim (2012) compared EEN and TPN in 56 patients following total gastrectomy. There was no significant difference in nutritional parameters, liver function, or complications between the two groups on post-operative day 7 after total gastrectomy. However, vomiting and abdominal distension were more frequent in the EEN group. There was a non-statistically significant small reduction in ICU stay in the EEN group of 12 versus 13 days compared to the TPN group \(^9\).

In a study of 150 patients undergoing oesophagectomy, Han-Geurts et al (2007) randomised patients to FJ or ND tube placement. The ND tube was removed from all patients on POD 1 or 2, and patients were allowed to drink 25 ml/hour. Full enteral feeding took three days to be established in both groups. There was a high rate of catheter-related complications, seen in 35% of patients with the FJ and 30% with the ND tube. Surgical complications were higher in patients with the ND tube 22% vs 32% with the FJ tube, while the incidence of non-surgical complications was similar in both groups \(^10\).

Problems continue once surgery is over: 90% of patients will lose at least 5% of their body weight at 3 months following surgery, while 16% will lose more than 15% of their body weight. Prolonged nutritional support can, therefore, be needed for weeks or months following surgery. During the first year after oesophagectomy, Haverkort et al (2010) reported that 78% of patients lost weight directly after the procedure and their mean body weight remained lower for the entire post-operative year \(^11\). Similarly, Ludwig et al (2001) reported that oesophagectomy patients without pyloroplasty or pyloromyotomy continued to lose weight in the immediate six months following surgery but regained weight thereafter up to 1 year \(^12\).
The advantages of an FJ are that up to 94% of patients can receive target nutritional requirements within 72 hours, and patients can be discharged home with ongoing feeding. However, both procedural and tube-related complications occur. Feeding jejunostomy tube insertion is the most common method to maintain adequate EN after oesophagectomy. However, there are a small but serious range of complications that can occur. Many patients are able to resume oral intake within a short period following surgery and are discharged with an FJ that is not used for nutritional support. Routine FJ placement at oesophagectomy may, therefore, place certain patients at avoidable risk.

Fenton et al (2011), in an assessment of feeding jejunostomy tubes during oesophagectomy, suggested that the only absolute indication for a feeding tube was low BMI, < 18.5 [13]. They recommended selective FJ placement based on the surgeon’s judgement [13]. Markides et al (2011) assessed five RCTs and one case control study including a total of 344 patients undergoing oesophagectomy [14]. There was a significant variation in the nutritional access routes used including intravenous fluid therapy, FJ, NJ and ND. No route was found to be superior to any other, and NJ and ND tubes were associated with a significant rate of dislodgement. Overall, the authors concluded that there was insufficient evidence to support a single feeding route in oesophagectomy patients. Following the publication of this review, a study by Barlow et al (2011) randomised 121 patients to EEN or control feeding (including nil-by-mouth, IV fluids, sterile water). Oral fluids and diet were introduced over two to five days. The median LOS was reduced in the EN group by three days, and there was significantly lower operative morbidity [15].

In conclusion, although there is a wide variation in practice, EN is superior to PN after oesophagogastric surgery. Early EN can be initiated from 6 hours post-operatively. However, the optimal route for EN has not been proven. Feeding jejunostomies are a useful adjunct to resection of oesophageal malignancy and are associated with minor complications which are mainly reversible. Up to 25% of patients will require feeding beyond 3 weeks, while 75% will have adequate oral intake at discharge. By one year, approximately 85% of patients will return to a normal or minimally restricted diet.

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DEBATE: TO FEED OR NOT TO FEED IN GI SURGERY

In favour of feeding:

John Drover
Queen’s University, Kingston
Canada

Professor Drover began by claiming that he would identify two measures of patient status that confer increased risk, he would list three measures that can be taken to improve outcome and two benefits of nutrition. His view was that these arguments were so compelling; they would make the case for the use of early feeding in GI patients.

There is substantial evidence to show that major post-operative complications are related to nutritional status. In 1987, Mughal and Memuid reported that pre-operative weight loss in patients undergoing major digestive surgery increased the risk for morbidity and mortality compared to well-nourished controls [1]. A Veterans Affairs study in 1991 demonstrated that increasing levels of malnutrition confer an increased risk of infectious and non-infectious complications [2], while Hackett (1979) showed that energy balance took around 12 days post-operatively to return to pre-operative levels, and that a patient’s final energy balance was associated with their previous home intake [3]. Patients with high energy outputs tend not to compensate by increasing consumption.

There are many predisposing factors that lead to malnourishment, which occurs in 15% to 60% of patients before surgery. There is the underlying disease itself, along with other chronic diseases, the influence of surgery, the physical insult to the digestive tract and prolonged or partial fasting due to loss of appetite or difficulties with eating.

In the past, the usual post-operative approach was to subject the patient to fasting and gastric decompression until normal bowel function resumed, followed by progressive reintroduction of diet once the gut was working. The aim of this was supposedly to “rest” the bowel.

Today we see a different approach. With increasing use of laparoscopy, much has changed in the management of these patients, with many patients now eating on the day after surgery. The concept that early nutrition can offer positive benefits to patients has been studied extensively. In 1990, Delmi et al studied the effect of 250 kcal supplementary nutrition in a group of elderly patients with femoral neck fracture. The patients receiving supplementation had significantly fewer severe complications and a significantly reduced length of stay compared to those on a control diet. Six months after the fracture, the complication rate and mortality were still significantly lower in the supplemented patients [4].

In a 2001 meta-analysis of 11 studies including 837 patients undergoing elective gastrointestinal surgery, early enteral feeding (EEN) was found to reduce the risk of any type of infection and mortality with no adverse effects on anastomotic healing [5]. The authors conclude that there is no advantage in keeping patients nil-by-mouth after elective GI surgery. The only adverse effect was increased vomiting in the EEN group. However, Gustafsson et al (2012) reported that this can be managed, particularly through interventions by the anaesthetist [6].
In another meta-analysis of 15 RCTs, and 1,240 patients, Osland et al (2011) looked at studies where EEN had been used in surgical patients. Most patients were undergoing colorectal surgery, either with laparoscopy or open surgery. Tube feeding was initiated on post-operative day 1 in four RCTs, while a regular diet was used in six studies on day 1, with a mixture of approaches in the other five. The cumulative result was that early feeding was favoured with a statistically significant reduction in risk for post-operative complications in EEN patients [7]. There was also a non-significant trend favouring EEN in respect of mortality, anastomoses, days to flatus, days to first bowel movement and length of stay, while nasogastric tube reinsertion was more common in EEN patients.

Finally, all of this evidence is incorporated within ERAS (Enhanced Recovery After Surgery) guidelines which recommend that patients be screened for nutritional status, that pre-operative fasting should be minimised and that post-operative food intake should begin as soon as possible, with the use of oral nutritional supplements if appropriate.

In summary: Professor Drover is in favour of feeding in GI surgery, whether or not this is delivered via a tube.

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Against (tube) feeding in GI surgery:

Johannes Zacherl
Herz-Jesu Krankenhaus Wien, Vienna
Austria

Professor Zacherl made a surprise announcement that he, too, was in favour of feeding in GI surgery, but that he was not in favour of using tubes, due to the extra morbidity they bring about.

The options for nutritional support in GI surgery are: parenteral nutrition (PN), jejunal tube feeding (JEJ), percutaneous endoscopic gastroscopy.
(PEG) - before or after cervical resection, nasojejunal (or duodenal, NJ/ND) tube feeding, and early oral feeding.

The drawbacks of JEJ, PEG and ND/NJ feeding include intolerance and diarrhoea, distension, site bleeding or GI bleeding, tube obstruction, reflux, rhinopharyngitis, nasal mucosa necrosis or otitis, catheter dislocation, peritonitis, small bowel volvulus, non-occlusive small bowel necrosis (NOSBN), or pneumatosis, and portal vein gas, all of which are well documented in the literature.

Anastomotic leaks can cause considerable morbidity and mortality after oesophagectomy, ranging from asymptomatic radiographic findings to necrotising thoracic infections \[1\]. These technical complications have a negative impact on survival following oesophagogastrectomy for cancer \[2\].

Han-Geurts et al (2007) also reported a high rate of complications related to tube feeding. There were minor catheter-related complications in 35% of patients with jejunostomy, and 21% in patients with a nasoduodenal tube. There were infections at the jejunostomy site in 16% of patients, and leakage in one patient that required re-operation. Up to 11% of patients required reduced feeding due to intolerance \[3\]. There were similar findings in a study of 205 patients undergoing oesophagectomy for malignancy. Ryan et al (2006) concluded that needle catheter jejunostomy (NCJ) was an effective method of providing nutrition post-operatively, but also reported three serious complications relating to the NCJ, one of which resulted in death \[4\].

Non-occlusive small bowel necrosis is a very serious complication that has been associated with early enteral nutrition. There are certain circumstances that predispose towards NOSBN, including low cardiac output, incomplete fluid resuscitation, hypotension, atherosclerotic vascular disease and congestive heart failure. However, the 1% incidence reported in one review caused the authors to question the routine operative use of early post-operative enteral feeding via NCJs or tube jejunostomies \[5\].

Professor Zacherl felt that there was serious under-reporting of this catastrophic complication, pointing to his own review of recently published studies which reported an incidence of jejunal tube-related NOSBN ranging from 0.15% to 5.88% with virtually 100% mortality in each case.

In an RCT involving 237 patients undergoing total gastrectomy for gastric cancer, Doglietto et al (2004) found no advantage of placing a nasojugal tube regarding major post-operative complications, overall post-operative mortality, passage of flatus, hospital length of stay, post-operative pain or abdominal distention \[6\]. Similar results were reported by Mazaki et al (2008), following a meta-analysis of 29 studies involving 2,552 patients undergoing elective GI surgery \[7\]. Their analysis found that, compared to PN, enteral nutrition (EN) was beneficial in the reduction of any complication, any infectious complication, anastomotic leak, intra-abdominal abscess and duration of hospital stay.

A study carried out on 447 patients undergoing major open upper GI surgery, randomised patients to receive either enteral tube feeding via a needle catheter jejunostomy, or normal food at will from the first day after surgery \[8\]. There was a significant reduction in time to resumed bowel function, total number of major complications, length of stay and rate of
post-discharge complications in the group allowed to eat normal food at will, leading the authors to conclude that this practice did not increase morbidity.

This begs the question as to whether it is necessary to introduce a jejunostomy, when good results have been obtained without? Wheble et al (2012) reviewed four trials in which patients undergoing oesophagectomy for cancer received immediate post-operative enteral feeding or waited until oral feeding could be established. All four trials concluded that routine post-operative enteral nutrition was feasible, but there was no evidence to suggest that it conferred any clinical benefit [9].

In conclusion, the tube site used for early feeding has the potential to bring about additional morbidity; early oral feeding results are comparable, or even slightly favourable, compared to tube feeding, while the main role for tube feeding is in patients where a swallowing disorder is anticipated. For routine procedure, early oral feeding, not tube feeding, should be introduced within an early recovery protocol, and if fluids can be started the day after surgery, there is no need for a tube.

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Int Cardiovasc Thor Surg (2012);15:709-12
HOW TO CONVINCE PAYERS: HEALTH ECONOMICS

Nicolas Demartines
University Hospital CHUV, Lausanne
Switzerland

Other speakers have already discussed improvements in surgical outcome, particularly those related to enhanced general management. There is plenty of evidence that the Enhanced Recovery After Surgery approach (ERAS) decreases morbidity and enhances recovery. If the patient is doing well after surgery, and if stress induced by surgery has been reduced, the consequence will be a decrease both in length of stay and costs.

Following colonic surgery, the goal is to have normal gastro-intestinal (GI) function with normal food intake and bowel movement as soon as possible. To achieve this goal, both pain and nausea should be controlled adequately.

In colorectal patients, Gustafsson observed a direct correlation between a high adherence to ERAS elements and a decrease in symptoms, 30 day morbidity, and readmissions [1].

Before the formal introduction of ERAS in our institution in May 2011, we complied with 54% of ERAS elements before, and 30% after, surgery. Following systematic implementation of ERAS, our institution is now 90% compliant before, and 58% after, surgery. Application of the ERAS protocol is known to reduce complications by 50%, and, therefore, decreases hospital length of stay (LOS) and cost [2].

An audit of ERAS outcome should be carried out at regular intervals to adapt and correct the compliance. An audit also demonstrates the decrease both in complications and LOS. Based on these data and a cost-benefit analysis, it can be demonstrated to the payers that the investment is reimbursed with an additional cost saving for the hospital.

Beginning in May 2011, we performed a precise cost-benefit analysis of ERAS implementation in our Department for Visceral Surgery, the results of which will be published soon.
After ERAS implementation, we observed a decrease in major complications and median LOS. Based on LOS only, we saw a cost saving, but to confirm this outcome, it was necessary to perform a comprehensive analysis based on real cost: a cost minimisation analysis. Fixed costs for the programme included multidisciplinary team training, a database for the audit programme, and a dedicated ERAS nurse, along with disposable costs for the additional nutrition (pre- and post-operative) and patient logbooks. In addition to savings on LOS, any costs relating to readmissions and management of complications were taken into account. Taking into account the fixed costs, our model shows that ERAS implementation is cost-saving as soon as 25 patients are included in the programme.

Our analysis shows that major savings were observed in medical and nursing care, with a significant decrease in medication, laboratory services and radiology. This is due to both the decrease in complications and the use of Care Maps. Full details of this analysis will be published soon.

Another study that focused on the effects of nutrition in a cohort of surgical patients drawn from the US national database, calculated $2,066 net cost savings per patient [3]. Chevrou-Severac reported that similar savings could be made with immunonutrition in a cohort of Swiss patients [4]. Savings ranged from 1,137 CHF to 2,598 CHF, depending on whether immunonutrition was given post-operatively or was begun earlier, before surgery.

From the payer perspective, the hospital needs to consider the additional cost of immunonutrition and the benefit in terms of reduced complications and LOS. However, it is debatable whether immunonutrition should be given to high-risk patients only, or to all patients before major surgery. The time frame for immunonutrition is also not clear, is it better to give it pre- or post-operatively, or both?

As well as alternative nutritional strategies, several other topics should also be considered: the baseline hospital infection rate, as this affects potential savings, and the nature of the hospital reimbursement system, but this is another study for the future.

In conclusion, nutrition according to ERAS principles is highly cost effective, decreases complication rates, saves money, and - although it may not be possible to put a cost on it - leads to happier patients and heightens the hospital reputation.

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PATIENT MOTIVATION AND COMPLIANCE: UNIT EXPERIENCE

Catherine Fleuret
Specialist Dietician, The Royal Marsden NHS Foundation Trust, London United Kingdom

Since the end of 2010, a cohort of patients undergoing surgery for gastric and oesophageal cancer have followed a version of the Enhanced Recovery After Surgery (ERAS) programme developed at The Royal Marsden Hospital. It was recognised, from the outset, that its success would depend on full support from the multi-disciplinary team (MDT) which included: surgeon, intensivist, dietician, nurses, physiotherapist, clinical nurse specialist, and the chief nurse. Input from these specialities was invaluable in creating a protocol that was both evidence based and workable.

The Figure below shows an abridged version of the ERAS MDT protocol, and illustrates the way in which the dietician is involved throughout the patient journey, from the initial assessment, through the pre-operative build up, into the immediate inpatient post-operative recovery period and during outpatient follow-up, which can extend to months.

The ERAS protocol is supported by documentation, including a MDT care pathway, which highlights the MDT and surgical roles from admission to discharge. From the nutritional perspective, the care pathway is enhanced by a day-by-day jejunostomy feeding regimen which ensures that the patients progress along the ERAS protocol.
The success of an ERAS protocol relies on both MDT teamwork and patient compliance \cite{1}. Patient engagement is crucial to the success of the protocol, so patients are introduced to the concept of the ERAS programme at their first surgical appointment. It is recognised that recall of a verbal consultation can be poor, while tailored written material can increase knowledge and patient satisfaction and reduce anxiety \cite{2}. Therefore, a patient information leaflet was produced by the MDT, with input from the Patient Advice and Liaison Service (PALS), outlining what the patient can do to prepare themselves for surgery, the role of the team in their preparation, and what to expect at surgery and follow-up.

Previous speakers have reviewed the evidence for nutritional intervention in malnourished patients, and have demonstrated that weight loss at diagnosis is an independent risk factor for post-operative complications \cite{3}. In contrast, regular intervention has been shown to minimise weight loss and deterioration in nutritional status during intensive treatment \cite{4}.

Furthermore, we know that nutrition is extremely important to cancer patients during their treatment \cite{5}. In a situation where they are subject to medical or surgical interventions, participating in their nutritional build-up can be empowering for them. Therefore, patients are seen by a dietician at their initial surgical appointment in order to engage them by highlighting the importance of nutrition in their overall treatment plan. We address existing nutritional problems and discuss issues they may encounter as their treatment progresses. Patients are then reviewed again following their neo-adjuvant chemotherapy where we discuss the concept of immunonutrition and dietary considerations post-operatively, including jejunostomy feeding where appropriate. It is hoped that, by seeing the patients at this early stage, we can correct nutritional problems and can build a good relationship that fosters compliance and motivation.

Immunonutrition and carbohydrate loading in the immediate pre-operative phase are a key aspect of the ERAS programme at The Royal Marsden. The supporting evidence has been discussed at length by previous speakers. The regimen involves immunonutrition (one sachet of Oral Impact\textsuperscript{®} three times per day in 250ml of water) for the five full days prior to surgery, as well as a carbohydrate drink on the morning of surgery. It can be an onerous regimen, so how are the patients responding to it? We know that patient compliance with nutritional supplements is variable \cite{6}, but there are a number of strategies which can improve compliance. These include providing supporting literature, offering a choice of flavours \cite{7}, encouraging and educating the patient and ensuring that supplements can be prepared easily \cite{8}.

Therefore, we have applied these principles to our approach with the patients. They are seen two weeks prior to surgery by the dietician, where the benefits of immunonutrition and carbohydrate loading are explained, flavour preferences are explored and administration of the product is discussed. In addition, the patient is given written information which includes a tick-box section to enable them to track their daily consumption, as well as a shaker to facilitate its preparation. The patients are provided
with the dietician’s contact number and counselled throughout this pre-operative period as required.

Data on compliance is anecdotal at present. However, patients generally tolerate immunonutrition well and find the combination of written literature and verbal instructions helpful. Our experience is supported by a small Japanese study of 23 patients which reported good compliance (82.6%) with the same prescription of immunonutrition, although the patients were admitted five days before surgery, which may have had an impact on their compliance [8].

It can be challenging to maintain compliance with an ERAS programme in the post-operative period, both for staff and patients [9]. In particular, patients can become frustrated with the speed of their recovery. The patient will see a dietician every working day during their inpatient stay, and we aim for it to be the same dietician that they met during their outpatient visits. A familiar face provides support and encouragement to the patient during this difficult period. Where a jejunostomy tube has been placed, independence in feeding is encouraged with a focus on preparation for discharge. It has been found that this helps to keep patients engaged and motivated in their recovery.

So far, the introduction of ERAS has brought positive results. A recent audit found a reduction in total length of stay (LOS) by three days. However, it is acknowledged that the audit involved small numbers and that changes in LOS cannot be attributed to any single change in practice. Patient experience and compliance have not been evaluated formally, but we are currently undertaking a patient experience survey which looks at patient opinion of, and adherence to, the programme. The survey has two parts: one is given at the first surgical appointment after discharge and focuses on their experience during the pre-operative build up and their inpatient stay, the second part is given three months after surgery and looks at functional status in recognition of the fact that surgery can impact quality of life for many months [10].

Future developments designed to help maintain staff and patient adherence to the ERAS programme include bedside posters on the critical care unit to track the ERAS pathway, and self-completed patient recovery diaries to enhance patient engagement in their rehabilitation.

In summary, successful implementation of ERAS protocols depends on staff and patient engagement. At The Royal Marsden, strategies have been employed to maximise compliance and motivation. In order to optimise the impact of dietetic intervention, the importance of nutrition is emphasised to patients at an early stage, expectations are addressed and managed and patients are reviewed by a dietician regularly. This input is enhanced with supporting resources and a MDT care pathway into which nutrition is fully integrated. As has been highlighted by previous speakers, an ERAS programme must respond to patient input and, therefore, patient experience surveys are being undertaken to inform the evolution of our ERAS programme.
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