PERI-OPERATIVE MANAGEMENT OF UPPER GI SURGICAL PATIENTS

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FOREWORD

*Issues in Professional Practice* (IIPP) is an occasional series of booklets published by the Association of Surgeons of Great Britain and Ireland to offer guidance on a wide range of areas which impact on the daily professional lives of surgeons. Some topics 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 Perioperative Management of Upper GI Surgical Patients represents the proceedings of a two-day international meeting held in Zurich in January and February 2014. 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 best clinical practice.

There was unanimous agreement that nutrition is an important component of protocols in upper GI surgery, and that all patients should undergo nutritional screening before major surgery. Furthermore, there is increasing support for the use of immunonutrition, both before and after surgery.

This booklet provides a series of brief summaries of each presentation given in Zurich. The topics cover high-risk surgery and outcomes, nutrition in surgery, EN access techniques, peri-operative optimisation, and finally, surgical outcomes improvement initiatives and practice-sharing.

The Association hopes that this publication, and others in the series (all accessible at: [www.asgbi.org.uk/publications](http://www.asgbi.org.uk/publications)), will provide concise advice and guidance on major current issues, and grow into a helpful and accessible resource to support your professional practice.

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

Professor John Primrose
President
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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 upper GI surgical pathways, 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.

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The meeting was accredited by the Association of Surgeons of Great Britain and Ireland and sponsored by Nestlé Health Science.
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PART 1: HIGH RISK SURGERY AND OUTCOMES

Chairs:
Dileep Lobo (UK)
William Allum (UK)

1.1 High risk surgery and complications: new ESICM definitions

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Queen Mary University of London, UK

Three factors can influence post-operative complications: the surgery itself, patient characteristics and the quality of the peri-operative care. Surgery, including the process of anaesthesia, involves tissue injury, which will inevitably lead to a systemic inflammatory response and its consequences. The effects of surgery can only be modified to a limited extent, for instance, by using minimally invasive techniques.

Patient factors that affect outcomes include age, fitness, co-morbidities and cardiac function. Although patients can be prepared for surgery through weight loss and smoking cessation, many other factors can only be modified to a small extent. Furthermore, surgery is routinely being offered to more and more patients, who possibly would not have been considered suitable in previous years, thereby increasing the risk of complications.

The biggest modifiable factor in the whole surgical process is peri-operative care, which can significantly affect patient outcomes.

The word “complication” is an emotive term, suggesting that an error or mistake has been made. However, what happens to the patient is often an inevitable consequence of surgery, rather than a complication. Inflammation will always follow tissue injury, but at what point does it become an infection? Respiratory impairment is almost inevitable following abdominal surgery with general anaesthesia, but is also part of a spectrum leading to pneumonia, differentiated only by degree of severity.

Complications have a significant impact on long-term survival. Khuri et al (2005) showed that the most important determinant of decreased post-operative survival was the occurrence, within 30 days of the operation, of a complication (see Figure 1) 11.

Independently of pre-operative patient risk, the occurrence of a 30-day complication reduced median survival by 69%.

Figure 1: Effect of complications on long-term survival

Although surgical mortality rates vary widely amongst hospitals, complication rates may be surprisingly similar. In a study on North American hospitals carried out through 2005 to 2007, risk-adjusted mortality rates for similar surgical procedures varied from 3.5% to 6.9%, while overall complication rates were 24.6% to 26.9% respectively [2]. However, the mortality of patients experiencing major complications was twice as high in those hospitals with very high overall mortality (p<0.001). While it may not be possible to prevent complications, the severity may be reduced with good peri-operative care.

Recent evidence from the UK suggests a “weekend” effect on hospital mortality, where the death rate for patients undergoing surgery on a Friday is higher than for patients undergoing surgery earlier in the week. This suggests reduced weekend provision of care may be a causal factor [3].

The concept behind peri-operative medicine is to prevent and treat any harm resulting from the tissue injury due to surgery and anaesthesia. A major problem in this area is amassing the evidence to support one intervention over another; clinical trials have been too small to influence practice, and have been variable in design, making it difficult to compare findings. Few of them have been patient-centred; 30-day survival is a common outcome measure, but is often not the one most relevant to patients themselves. A recent trial in patients undergoing hip replacement was unusual in using ability to walk as an outcome rather than 30-day mortality [4]. Trials use a range of outcome measures that are rarely pre-defined and do not incorporate any concept of severity.

To resolve some of these issues, the Outcomes Measures Taskforce has been established. The aim of the group is to develop clear robust definitions of outcomes measures that are suitable for use in large scale trials and are comparable across geographical boundaries. If standardised measures are used, evidence can be built up from multiple studies.

The aim is also to address economic as well as clinical outcomes; peri-operative medicine can save money by reducing complications, demonstrating that good quality care does not have to be expensive.

Following a large literature search, it was found that there were many valid approaches recorded in the literature. The Task Force has brought together a number of groups to work collaboratively and the standards document produced from the exercise will not be definitive, but will promote debate in the area. The main aim is to get people who have not used these tools before to begin using them.

1.2 Dindo-Clavien classification of post-operative complications

Nicolas Demartines
University Hospital CHUV, Switzerland

Two reports publishing outcomes of the Whipple procedure illustrate the importance of using standard classifications. The papers by Trede et al (1990) and de Oliveira et al (2006) report widely varying complication rates of 18% and 59% [5,6], with the difference being due to the way in which the complications are classified.
In a meta-analysis of 199 papers reporting short-term outcomes following major surgery (pancreatectomy, oesophagectomy and hepatectomy), Martin et al (2002) found major inconsistencies and gaps in the reporting of complications [7]. Twenty-two per cent of papers did not report follow-up outpatient information, 34% did not provide a definition of the complications, 20% did not supply information on severity grade used and risk factor analysis was lacking in 29%.

In a review of post-operative mortality following gastrectomy surgery, there were major differences in the way in which mortality was reported: 30-day mortality (40), in-hospital death only (14), no definition (31) and other (10) [8]. A similar problem regarding the definition of anastomotic leak was identified in a systematic review of 97 studies reporting outcomes of oesophagogastric, hepatopancreatobiliary and lower gastrointestinal surgery, in which the researchers found 56 different definitions using a combination of clinical features and radiological investigations.

In 2005, Bassi et al noted that the definition of post-operative pancreatic fistula varied widely between centres, and reported on a process of agreeing an objective and internationally accepted definition [9]. The original proposal to classify the complications of surgery, and to differentiate complications, sequelae and failures, was made in 1992 by Clavien [10]. A classification of complications was made based on four grades ranging from Grade 1, with no lasting disability, to Grade IV, indicating death as a result of the complication.

In 2004, Clavien and colleagues critically re-evaluated and modified this original classification system to increase its accuracy and acceptability to the surgical community [11]. The new system was still very reliant on the therapy used to treat the complication. The classification was tested in 6,336 patients undergoing elective surgery, and it was found to correlate significantly with the complexity of surgery (p<0.0001) and the length of hospital stay (p<0.0001). The system was considered to be simple, reproducible, logical, useful and comprehensive.

Five years later, a critical evaluation of how the classification had been used in the literature found that there had been a dramatic increase in its use with a reduction in the use of subjective terms [12]. In the same period, the scheme had received over 2,500 citations from all areas of surgery (see Figure 2). In the study, 11 difficult clinical scenarios were independently assessed to test the accuracy and reliability of the classification, resulting in a high degree of agreement.

**Figure 2: Increase in citations since publication of the critical review**

**Classification of Complications**

Citations

- 1992
- 2004

>2500 citations (until end of 2013)

Clavien, Ann Surg 2009
Of course, any assessment is only as good as the quality of the original data. In an evaluation of the validity of recorded data, an audit was conducted of a quality assessment database in a centre in Zurich. Pre-operative risk factors of each patient were recorded by residents, along with a grading system to track complications. After three months, the results were disclosed and residents were subjected to a training course. Following this, the audit was continued for three months with disclosure to the residents. It was found that residents failed to report most complications; 80% and 79% in the two periods. Co-morbidities were incorrectly assessed in 20% of patients in the first period and 14% in the second. However, 97% of complications that were recorded were correctly graded.

The effect of complications on overall costs is significant. In an analysis by Vonlanthen et al. (2011), the full in-hospital costs in a high-volume tertiary centre were collected for 1,235 patients undergoing various abdominal procedures between 2005 and 2008. Patients who experienced no complications had mean costs per case of $27,946. Costs increased dramatically with the severity of the post-operative complication, reaching a mean cost of $159,345 for patients with grade IV complications, a five-fold increase. It is clear that the cost of a severe complication is much greater than the cost of the original surgery. The investigators found that the complications were organ-specific, being more common in patients undergoing pancreas surgery.

In conclusion, there is a need for standardised outcome reporting, with definitions of specific complications agreed by specialised societies. Furthermore, the collection of data on complications is too important to be left to residents, and requires the expertise of an independent data manager.

### 1.3 Complications after oesophageal surgery: International working group RGG

**Donald Low**  
*Director Thoracic Surgery and Thoracic Oncology, Virginia Mason Medical Center, Seattle, USA*

Although it is often believed that high volume institutions have lower rates of surgical mortality, this is not necessarily true for all procedures. Birkmeyer et al. (2002) showed that mortality decreased as volume increased for 14 types of procedure, but that the absolute differences can be as low as 0.2% for procedures such as carotid endarterectomy.

A 2011 study looked at trends in hospital volume and operative mortality for US patients undergoing eight different high-risk procedures during the period 1999 to 2008. Although operative mortality fell in high volume units, the authors concluded that the decline in mortality was largely attributable to a variety of factors, not just high volume.
The link between volume and outcome was supported by a 2012 publication that reviewed outcomes of 27,843 oesophagectomies conducted in low and high volume surgical units. Low volume institutions had higher in-hospital and 30-day mortality (8.48% vs 2.82% and 2.09% vs 0.74% respectively). Inclusion of 90-day mortality data nearly doubled the rate.

A review summarising the reporting of complications of oesophageal cancer surgery looked at 122 papers reporting the outcomes of 57,299 oesophagectomies. Ninety-four per cent of the papers recorded mortality but with numerous different definitions, and 60% did not define any of the measured complications. Twenty-two different definitions of anastomotic leak were used and, of 115 papers reporting post-operative mortality rates, 25 defined the term using 10 different definitions.

In a review of short-term outcomes following oesophagectomy at 164 US hospitals, the authors found a 161% difference in mortality between high and low volume units. They concluded that, after controlling for case mix, outcomes were affected by other aspects of hospital quality beyond the surgery [16]. But the system for recording complications makes it impossible to allow assessment of differences and, therefore, to improve.

Complications are the single greatest factor increasing resource utilisation and costs in the treatment of oesophageal cancer, but there is no standardised approach to documenting the complications associated with oesophagectomy. Blencowe suggested that a “core outcome set” should be defined and used in all studies reporting on oesophageal cancer surgery [17].

A systematic review of the benefits and risks of neoadjuvant chemoradiation for oesophageal cancer highlighted the difficulties of working without standard definitions [18]. Thirty-eight studies were included, but chemoradiation-related toxicity was reported in only ten, which used differing systems, giving widely varying rates of that incidence of complications, from 28% to 73%. Post-operative morbidity was also not uniformly reported, making it difficult to assess whether the risks outweighed the benefits.

In a review of the outcomes comparing the results of an open versus minimally invasive oesophagectomy, half of the 16 studies did not report overall morbidity or individual complications, such as cardiac arrhythmia [19].

Numerous studies report the impact of complications on mortality, length of hospital stay, overall costs, survival in cancer surgery and quality of life. Viklund et al (2005) reported that surgery-related complications were the main predictor of reduced QoL at 6 months post-operatively [20]. The surgery itself was found to have no effect on QoL.

What would an ideal classification system look like? Classifications should be objective and not open to interpretation by caregivers or data managers. They should be simple to apply, reproducible, logical, useful and comprehensive. Various specialist groups have already begun the
process, and have proposed definitions of post-operative pancreatic fistula and delayed gastric emptying [9 - 21].

Two different grading systems are available, which are very similar in approach, and which can stratify the risk and the invasiveness of the therapy required to manage the complication [11 - 22]. An assessment of patients with complications following oesophagectomy for cancer found that the Accordion Severity Grading System for grading complications correlated well with resource use in terms of treatment costs and length of stay (see Figure 3) [22].

The Esophageal Complications Consensus Group (ECCG) is a group of 21 surgeons from around the world, which has the aim of producing a basic list of complications, as well as a group of quality parameters which should be collected, associated with oesophageal resection. All assessments of the current datasets of the members of the ECCG showed significant variability, with some centres using only three types of pulmonary complications, while some record up to 28. Of the 21 centres, only five routinely classify severity.

The first output is a basic list of complications linked to various definitions, such as the CDC system. A list has also been drawn up of the other essential outcome or quality measures that should be prospectively collected in institutional databases and national audits. The group is currently producing a standardised system for defining key complications.

The ultimate goal is to find a common language for reporting complications: to provide a standardised international infrastructure for recording and reporting complications and adverse events associated with oesophagectomy.

**Figure 3: The effect of complications on the costs of oesophageal resection**

<table>
<thead>
<tr>
<th>Complication</th>
<th>n</th>
<th>Cost $</th>
<th>LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastomotic leak</td>
<td>11</td>
<td>57463*</td>
<td>18.5*</td>
</tr>
<tr>
<td>Atrial Arrhythmia</td>
<td>46</td>
<td>37284*</td>
<td>11.1*</td>
</tr>
<tr>
<td>Post-op delirium</td>
<td>37</td>
<td>39540*</td>
<td>12.9*</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18</td>
<td>40699*</td>
<td>12.8*</td>
</tr>
<tr>
<td>No complications</td>
<td>141</td>
<td>27686</td>
<td>8.7</td>
</tr>
</tbody>
</table>

* p <0.001

The effect of complications on the costs of oesophageal resection.
PART 2: NUTRITION IN SURGERY

Chairs:
Jens Kondrup (Denmark)
Donald Low (USA)

2.1 Pre-operative carbohydrate treatment: What is the evidence?

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Surgery is a traumatic process and, in the past, we have made it worse by starving, stressing and drowning our patients on the basis of very little evidence. The practice of routine fasting of surgical patients developed from a single case report in 1848 of a woman patient who aspirated and died while undergoing a Caesarean section. In 1883 Lister suggested that, if solid food in the stomach was to be avoided, patients should at least be given some broth, but his proposal was ignored.

The stress caused by surgery is significant: insulin sensitivity decreases, there is increased protein degradation, an impaired anabolic response, an increase in free fatty acids and increased expression of inflammatory genes. Starving has been found to enhance these responses. In a group of healthy volunteers, after 12 hours of starvation, there was a significant 29% fall in liver glycogen and a fall in liver lipids [23]. Re-feeding with a carbohydrate drink only partially reversed these changes (see Figure 4).

Insulin resistance is a process in which cells fail to respond to the normal actions of insulin, leading to reduced uptake of glucose, amino acids and fatty acids, inhibition of glycolysis leading to hyperglycaemia and the consequent adverse health effects. As long ago as 1887, Claude Bernard noted that hyperglycaemia was a reaction to stress, while in 1974, Äärina demonstrated that glucose intolerance was seen in surgical patients, particularly during and four hours after surgery [24]. Black et al (1982) were the first to report insulin resistance after traumatic injury [25], while Ljungqvist et al (1994) demonstrated that glucose infusion, instead of fasting, reduced postoperative insulin resistance [26].

In 2008, Crossland et al used an animal model to investigate the effect of sepsis on insulin sensitivity [27]. In sepsis, the normal carbohydrate

![Figure 4: Changes in liver glycogen and lipids during fasting](image-url)
oxidation pathway is disrupted; the conversion of Akt1 to FOXO (forkhead transcription factor) is blocked, leading to increased pyruvate dehydrogenase kinase 4 (PDK-4) expression, decreased pyruvate dehydrogenase complex activity and decreased carbohydrate oxidation.

In a later study (2001), Ljungqvist et al noted that the changes in glucose metabolism during surgery were similar to those seen in type 2 diabetes [28]. Thorell et al (1999) showed that the development of insulin resistance is proportional to the magnitude of the operation, increasing from laparoscopic cholecystectomy to major colorectal surgery, where the fall in insulin sensitivity was 80% [29]. The peak fall in insulin sensitivity is seen on the first post-operative day and it can take up to three weeks to return to normal (see Figure 5).

Insulin resistance has an effect on morbidity. For each unit decrease in insulin sensitivity there is a significant increase in major complications, severe and minor post-operative infections [31]. Kiran et al (2013) investigated the post-operative glucose levels of 2,447 non-diabetic patients undergoing colorectal surgery [31]. Nearly 67% of patients experienced hyperglycaemia, and it was found that the degree of hyperglycaemia correlated with ASA class, surgical severity as measured by blood loss, infectious and non-infectious complications and mortality.

Insulin resistance can be modified by giving the patient a carbohydrate drink before surgery, but it must contain complex carbohydrates in order to have a sufficiently long action of duration [32]. Safety data has shown that the risk of aspiration is not increased through the use of pre-operative carbohydrate loading. Over 4,000 patients in clinical studies of surgical patients, and over 3 million patients in surgical practice, have been treated in this way without an increase in adverse events being reported. Pre-operative carbohydrate drinks convert the patient from a state similar to type 2 diabetes back to a normal physiological state with improved insulin sensitivity and peripheral glucose uptake [28-33].

In clinical terms, carbohydrate loading can mitigate the effects of major operations such as colorectal surgery, so that they have the same effect on insulin resistance as more minor operations [34,35]. Carbohydrate loading works by enabling the Krebs cycle to function effectively, leading to improved oxidation of carbohydrate [36]. Wang et al (2010) suggested that pre-operative carbohydrate loading stimulates the PI3K/PKB signalling pathway (phosphatidylinositol 3-kinase/protein kinase B), thereby improving post-operative insulin resistance [37].
In a recent meta-analysis of 21 RCTs involving 1,685 patients (733 with carbohydrate loading), Awad et al (2013) found that, overall, despite the poor quality of some studies, there was a significant drop in post-operative insulin resistance if the patient was given pre-operative carbohydrate loading [38]. Two studies showed no difference, and one study did not measure insulin resistance. However, there was no significant difference in post-operative complications. There was also no decrease in hospital stay for all patients, but there was a more pronounced difference for cases of major abdominal surgery. When carbohydrate loading is combined with other measures in the ERAS protocol, there is a 2.5 day reduction in LOS, a lower risk of complications, and no increase in readmission rates [39].

In conclusion, pre-operative overnight fasting is an obsolete practice. Patients should eat normally up to 6 hours before surgery, and take a carbohydrate drink up to 2 hours before. A nil-by-mouth rule is not a guarantee of an empty stomach, and free fluids reduce the risk of pre-operative dehydration. Pre-operative carbohydrate drinks are as safe as any clear fluid and may decrease complication rates, although this is not certain. LOS following abdominal surgery may be reduced. Although the effects may seem marginal, when combined with ERAS principles they can have a powerful effect.

2.2 Immunonutrition: Evidence review in GI surgery
Nicolas Demartines
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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 [40]. 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% [41].

It is difficult to identify which of the components of these programmes 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, as observed in prospective studies.

**Schiesser** (2008), among others, pointed out a direct relationship between peri-operative malnutrition and post-operative complications [42]. 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, concluding that it was a simple and reproducible tool, with a good distinction between the various levels of risk and good correlation with risk for complications (see Figure 6).

Despite these and other data on the role of nutrition in recovery after surgery, a survey of 77 hospitals in Switzerland and Austria revealed that selective nutritional support in hospitals was modest at best [43]. 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 undertook nutritional screening.

Of those who did carry out nutritional screening, 20% to 30% performed screening after surgery only, which was 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 antioxidants 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 [44], and one in 2011 of peri-operative arginine [45]. In addition, there have been two investigations into the cost-effectiveness of immunonutrition, one carried out in the USA and one in Switzerland [46, 47], and two papers on the subject, including a consensus statement from the North American Surgical Nutrition Summit, have appeared recently [48, 49].

**Marik et al** (2010) reviewed data for 1,918 patients from 21 studies, covering the period 1992 to 2008 [44]. 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 [45]. 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 \[47\]. 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 \[46\]. 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 published recently \[50 - 52\]. 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 \[53\]. 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.

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.

2.3 Early post-operative nutrition support: Separating data from dogma

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It is generally agreed that energy and protein deficits are associated with a poor post-operative outcome and can be reduced with EN, or a combination of EN and PN. But a number of questions remain: Does supplementary nutrition prevent accelerated catabolism of muscle in
the post-operative patient? What is the optimal amount of EN to use? Which patients need nutritional therapy in the post-operative setting?

In addition to the many well-known benefits of early EN, new factors have appeared in recent years, relating to the cholinergic anti-inflammatory pathway. By delivering nutrients to the gut, it is possible to regulate cytokine production in the gut wall and inhibit inflammatory response \[^{[54]}\]. Lipid-rich enteral nutrition prevents early loss of the gut barrier, enterocyte damage and local intestinal inflammation \[^{[55]}\].

In a study to investigate the response to endotoxaemia, 18 volunteers received placebo, control feed or high protein and high lipid feed EN followed by \textit{E coli} endotoxin to simulate metabolic stress. The EN group displayed a rapid anti-inflammatory effect, with the lipid and protein-rich nutrition modulating the immune response \[^{[54]}\].

A prospective study on 1,100 patients who had experienced blunt trauma, divided the patients into five groups according to caloric intake \[^{[56]}\]. Those with the highest enteral calorie intake had an increased incidence of ventilator-associated pneumonia (VAP) but the lowest incidence of bacteraemia. Those who received PN had higher levels of bacteraemia and VAP. The conclusion was that it is better to employ moderate enteral intake in the first week after injury and avoid PN.

\textbf{Rice et al} (2012) compared initial low-volume trophic enteral feeding with full enteral feeding in patients with acute lung injury for a period of up to six days \[^{[57]}\]. There was no significant difference between the groups in terms of ventilator-free days, 60-day mortality or infectious complications. In a 12-month follow-up, there was no difference in outcome between patients who were delivered 25\% or 80\% of their goal calories in the initial days \[^{[58]}\]. However, the study population was relatively healthy, and very ill patients had been excluded. A short-term ICU diet of 25\% of goal calories is unlikely to have adverse effects, and the quantity of feeding is probably less important than being fed early. The level of fluids may be more critical in Acute Respiratory Distress Syndrome (ARDS) \[^{[57]}\].

Should trophic feeding be extended to all patients? In a meta-analysis, \textbf{Choi} (2014) of four RCTs, involving 1,540 patients, no difference in mortality or ICU LOS was found between patients fed with trophic feeding or full feeding \[^{[Choi \ 2014 \ in \ press \ Critical \ Care]}\].

In the absence of EN, \textbf{Marik} noted that there is a progressive atrophy of the villous height and crypt depth leading to increased permeability and decreased IgA secretion \[^{[59]}\]. Animal data show that even a small amount of trophic feed (minimum of 15\% to 35\% of goal calories) can help to preserve the villus \[^{[60]}\].

In a study of the safety and optimal timing of EN, 32/100 patients with open abdomen received immediate EN, while 68 had initiation delayed by at least 36 hours. EN in these very ill patients was found to be safe, with no delay in fascial closure (6.47 vs 8.55 days), no difference in
multi-organ failure, length of ventilator days, ICU days, hospital days or mortality. In fact, there was a significant reduction in pneumonia in the EN group (p=0.008), (see Figure 7) [61].

Collier et al (2007) also reported positive results. In a retrospective review of trauma patients with OA, those who had EN initiated within four days had better closure rates within eight days (p=.02), lower rates of fistula formation (p=.05) and hospital charges which were reduced by more than $50,000 [62].

In a study of 1,174 haemodynamically unstable ICU patients requiring vasopressors to maintain blood pressure, Khalid et al (2010) compared those patients receiving EN within 48 hours (707) and those who did not (467) [63]. All required mechanical ventilation for more than two days. Mortality was lower in the early EN patients (22.5% vs 28.3%, p<0.001) with greatest benefit noted in the sickest people.

A number of studies have investigated the outcomes associated with early EN in high risk patients. In a prospective RCT of early EN in 121 patients undergoing major upper GI surgical resection, patients were randomised into groups receiving early EN (64) or control diet post-operatively (nil by mouth and IV fluid, 57). A lower incidence of wound infection (p=0.017), chest infection (p=0.036), and anastomotic leak (p=0.055) was noted in the early EN group and significantly shorter LOS [64].

In a 2011 meta-analysis, Doig et al reported that early EN in trauma patients requiring intensive care reduces mortality [65]. However, overall quality and patient numbers were low.

Despite the evidence, early EN is not used routinely. A lack of understanding of the potential benefits and information overload may play a part, with over 400 trials published on peri-operative nutrition. There may also be residual concern about complications such as aspiration, ischaemic bowel, and anastomotic leaks. In a survey of critical care nurses, other barriers were identified including a lack of feeding pumps, priority for other aspects of care, lack of enteral formula and dietician support [66].

New SCCM/ASPEN guidelines on the use of EN protocols are currently in review, and expected late 2014. The guidelines are based on the results from nine studies, and recommend that EN protocols should be used, as they increase the overall percentage of goal calories provided.
In the ICU setting, a lack of mobility and exposure to endotoxins puts patients at risk. A decrease in synthesis and an increase in catabolism leads to acute skeletal muscle wasting. In a study of 63 critically ill patients, Puthucheary et al (2013) observed a decrease in muscle cross section and muscle fibre, with myofibre necrosis being seen in more than 40% of the patients. Patients lose muscle in the ICU despite receiving adequate nutrition [67].

Resistance exercise increases nutritive blood flow to muscle, lowers insulin resistance, increases nutrient uptake, and may decrease myofibre necrosis, adding to the benefits of nutritional support. Numerous studies have shown the benefits of an early mobilisation and exercise programme, in terms of enhanced recovery and earlier discharge.

In summary, to date, multiple studies and more than adequate data suggest that EN in the peri-operative period is beneficial, and that early EN is better than later EN. In addition, it is clear that EN is superior to PN. Early EN should be used as a therapeutic intervention focusing not only on the nutrient delivery but as a metabolic modulator following surgical stress. The timing of PN supplementation is not yet clear. The quality of nutrition appears to be more important than the quantity, but over-feeding should be avoided. Protocols and guidelines accelerate enteral access, increase the delivery of nutrients and improve outcomes, but clinical judgement should always take precedent over a protocol.

2.4 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 [68, 69].

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 [70]. Toxocities due to chemotherapy also impact 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 [71-74].

Does 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 \[75\]. 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 \[76\].

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 leukopenia grade 3 of 17% vs 41% (ns) and neutropenia grade 3 incidence of 36% vs 66% \(p=0.005\) \[77\].

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 Odds 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 \[78\].

Cisplatin reduces plasma ghrelin levels through the 5-HT receptor, which may cause GI disorders and hinder chemotherapy. In trial, patients with oesophageal cancer receiving cisplatin-based neoadjuvant chemotherapy were randomly assigned to receive synthetic human ghrelin or saline \[79\]. After one week, patients receiving ghrelin had significantly higher food intake and appetite and fewer adverse events during chemotherapy than those in the placebo group (see Figure 8).

In a study of patients receiving neoadjuvant chemotherapy for oesophageal cancer, it was found that baseline Th1/Th2 balance (type 1 and type 2 CD4-positive T cells) predicts the severity of neutropenia and EN significantly reduced the decline of monocyte HLA-DR expression \[80\].

We have found that it is also best to implement supplemental 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 [81].

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 [82, 83]. In humans with lung cancer, fish oil was found to prevent deterioration of weight and muscle mass during chemotherapy [84].

Based on these findings, we 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.

2.5 Refeeding syndrome

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Department for Endocrinology, Diabetes and Clinical Nutrition
Inselspital Bern, Switzerland

Re-feeding syndrome (RFS) is a life-threatening condition characterised by severe intracellular electrolyte shifts, acute circulatory fluid overload and organ failure resulting from over-rapid or unbalanced re-feeding of a malnourished catabolic patient.

RFS is prevalent in about 10% of patients with gastrointestinal fistulae [85], 14% of elderly patients [86], 25% of cancer patients [87], 48% of malnourished patients [88], and 28% of patients affected by anorexia nervosa [89]. The hallmark is hypophosphataemia, which is seen in 55% of patients three days after re-feeding has begun [89].

Starvation or malnutrition leads to a catabolic state in which there is down-regulation of insulin and increased glucagon [90]. Subsequent gluconeogenesis and proteolysis mean that patients lose weight, and vitamin and mineral stores are depleted. Too rapid feeding, particularly with carbohydrates, leads to increased glucose lipogenesis, thiamine levels drop and a hyperosmotic state develops. Transcellular shifts of glucose and minerals can also take place leading to spasms, tetany and cardiac arrhythmias.

Clinically, the most important symptoms are tachycardia, tachypnoea and oedema. If pulmonary embolism can be excluded, these symptoms
suggest RFS. Thiamine is necessary for correct functioning of the glucose metabolism pathway leading to the Krebs cycle (see Figure 9). Without thiamine, the pathway is diverted to the development of lactate, leading to lactate acidosis via the Cori Cycle.

Clinical guidelines provide criteria for determination of patients at risk of RFS \[91\].

![Figure 9: The role of thiamine in glucose metabolism](image)

<table>
<thead>
<tr>
<th>One of the following</th>
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<tr>
<td>BMI &lt; 16kg/m2</td>
<td>BMI &lt; 18.5kg/m2</td>
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<tr>
<td>Unintentional weight loss of more than 15% in the preceding 3 to 6 months</td>
<td>Unintentional weight loss of more than 10% in the preceding 3 to 6 months</td>
</tr>
<tr>
<td>Very little or no nutritional intake for more than 10 days</td>
<td>Very little or no nutritional intake for more than 5 days</td>
</tr>
<tr>
<td>Low levels of serum magnesium, phosphate or potassium prior to feeding</td>
<td>History of alcohol or drug abuse</td>
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Other patients at risk include those on hunger strike, with anorexia nervosa, patients who have undergone bariatric surgery, short bowel syndrome, oncology patients and the frail elderly.

RFS can be confirmed by looking for severely low electrolytes (phosphate, magnesium or potassium), fluid overload (peripheral oedema or acute circulatory fluid overload) and disturbance of organ function (respiratory failure, cardiac failure or pulmonary oedema) \[92, 93\].

NICE Clinical Guidelines for the management of re-feeding syndrome recommend a carefully managed reintroduction of feeding with controlled step-up over a few days of energy, electrolyte substitution, fluid and micronutrients \[94\].

Since 1990, studies have been published containing guidelines for the management of RFS. Since the publication, in 2006, of the NICE guidelines, the recommended energy intake has halved but the evidence is low, only Grade D.

Of all the possible predictors for RFS, starvation is the most reliable. Positive correlation has been found with low magnesium levels before re-feeding, with pathological weight loss of >15% or with poor intake for more than 10 days \[92\].
Due to lack of evidence, many questions remain about the management of RFS. Is the recommended energy step-up regime too cautious? Unfortunately, published statements are conflicting, so it is difficult to know the optimum approach. Is the electrolyte regime correct and, if so, should they be given prophylactically? Many of these questions can only be answered by a large trial, randomised and controlled.

2.6 Report on the North American Summit on Peri-operative Nutrition

Robert Martindale
Division of General Surgery
Oregon Health and Science University, Portland, Oregon, USA

In 2012, nineteen participants from various surgical specialties held a summit meeting to discuss nutrition therapy of the adult patient anticipating major elective surgery. The aim of the meeting was to consider assessment and timing for pre-operative nutrition; peri-operative nutrition including carbohydrate loading and early EN; post-operative nutrition and the best way to implement nutrition strategies. Participants were asked to assess the evidence for and against peri-operative nutrition; to define high risk patients who might benefit from nutritional therapy; to identify areas that need further study or evidence, and the barriers to implementing peri-operative protocols.

In 2011, a Swiss-Austrian survey of 173 surgical departments found that surgical nutrition is largely neglected. Although the majority of respondents agreed that nutrition can decrease complications and length of hospital stay, only 20% carried out routine screening, and even fewer used the NRS system.

A NSQIP 2012 publication revealed that 30 day readmission rates were due to GI complications (27%), SSIs (21%), and 19% directly for malnutrition-related reasons. Overall 67% of readmissions are directly or indirectly due to nutrition.

It has been reported that appropriate and timely nutrition therapy has beneficial effects. Early EN can decrease mortality and infectious complications, maintain the mucosal barrier and attenuate the metabolic response to surgical stress. Specific nutrients, such as fish oils and arginine, positively affect membrane stability, immune function, and appropriate use of these specific nutrients can attenuate loss of lean body mass in surgical and critical care stress.

Many high risk procedures have been found to benefit from pre-operative risk reduction (see Figure 10).

Figure 10: High risk procedures that could benefit from pre-operative risk reduction

- Complex or re-operative colorectal (20-30%)
- Major UGI surgery (gastric, esophageal) (22%)
- Abdominal wall reconstruction (18-30%)
- Pancreatic (14-22%)
- Major hepatobiliary (11-19%)
- Major head and neck surgery (>T3 lesions) (8 to 14%)
- GU (ex:-cystectomy, prostatectomy, nephrectomy) (10 to 20%)
- Major re-operative or trauma orthopedics
- Spine procedure with hardware placement
- GYN (usually malignant disease)
- Major cardiothoracic
- Others selective by individual patient / procedure
In the pre-operative phase, a number of studies support EN in malnourished patients \(^9\), patients with obstructive jaundice \(^{96}\), head and neck cancer \(^{97}\) and GI cancer patients \(^{98}\). A larger prospective RCT provides stronger evidence \(^{99}\). Of the 1,085 patients recruited, 512 were at nutritional risk. Of the 120 patients with NRS \(\geq 5\), the complication rate was significantly lower in the group that received pre-operative nutrition, compared to the control group: 25.6\% vs 50.6\% (p=0.008). The post-operative hospital stay was significantly shorter in the pre-operative nutrition group: 13.7 vs 17.9 days (p=0.018). No benefit was seen in patients with NRS 3 to 4, suggesting that nutrition has an optimal effect in those at highest risk.

What surrogate markers or assessment tools are there which can help identify those who need nutrition? A large prospective Veterans Affairs study in the US involving 87,078 patients found that pre-operative serum albumin level is the best marker and most predictive of post-operative mortality along with 31 other pre-operative variables \(^{100}\). Kudsk (2003) also found that pre-operative albumin correlated inversely with complications, length of stay, post-operative stay, ICU stay, mortality and resumption of oral intake \(^{101}\). It is important to note that no markers currently available actually measure nutrition status and that only surrogate markers are available.

The role of pre-operative exercise therapy on post-operative outcome was also looked at. In a systematic review of 12 studies, Valkenet found that pre-operative exercise reduces complication rates and LOS following cardiac and abdominal surgery \(^{102}\). In an RCT of 95 patients undergoing colorectal surgery, functional capacity could be improved with several weeks of pre-operative therapy \(^{103}\). Finally, Li et al (2013) found that a one month “pre-habilitation” programme improved post-operative functional recovery \(^{104}\).

In a meta-analysis of the peri-operative use of arginine supplemented diets \(^{45}\), 35 articles were identified that compared pre- and post-operative nutrition vs either on their own. Overall, there was a significant reduction in overall infections and hospital length of stay but no reduction in mortality. The greatest effect was seen when nutrition was given both pre-operatively and post-operatively. This study was confirmed by another meta-analysis of immune modulating nutrition in the surgical population, reporting similar results of reduced infectious complications and length of stay \(^{51}\).

The traditional approach to post-operative feeding has involved waiting for bowel sounds before initiating feeding. The mechanism for post-operative ileus is now well characterised with a neurogenic phase, followed by an immunological phase that can last for a number of days. Any major intervention up-regulates ICAM-1 on the endothelium of the muscularis vasculature, setting off an inflammatory response and a decrease in contractile response \(^{105}\).

However, numerous studies have shown that early post-operative feeding can be carried out safely without waiting for bowel sounds. Several studies of early enteral feeding showed that feeding within the
first two days resulted in lower infection rates, reduced LOS, and decreased mortality and morbidity.

The role of immune and metabolic modulating for mulae was assessed in a meta-analysis of 26 RCTs, involving 2,496 patients undergoing open GI surgery. The results showed that 5 to 7 days of feeding were required to show benefit [51].

Following the collection of evidence, the participants developed consensus recommendations. The summit agreed that there was a need to follow a timeline throughout surgery with greater emphasis on pre-operative assessment and intervention in high-risk surgical populations. This assessment should include serum albumin levels (risk \( \leq 3.0 \text{mg/dL} \)) and C-reactive protein as surrogate markers for inflammation and nutrition. Additional high-risk populations included those with BMI \(<18.5\) or \(>40\), body weight less than 90% of ideal body weight, and history of weight loss prior to assessment.

Patients anticipating major elective surgery should be offered pre-operative immune and metabolic modulating formula. Isotonic glucose solution prior to major elective surgery and in the morning of surgery should be considered, and protocols for nutrition intervention should be developed [49].

Future directions for discussion by the group include peri-operative optimisation, the need for better nutrition screening methods, control of the inflammatory response, regulation of protein synthesis and breakdown, study of specific nutrients to find which ones work best, resistance exercise in the post-operative setting, and new attention to gut microbiology [49].
PART 3: EN ACCESS TECHNIQUES

Chairs:
Arved Weimann (Germany)
Riccardo Rosati (Italy)

3.1 The use of percutaneous radiological gastrostomy in oesophageal cancer patients: A debate

FOR THE MOTION:

Christophe Mariette
University Hospital Lille, France

As malnutrition is present in up to 80% of patients with oesophageal cancer, and dysphagia and cancer-induced anorexia are worsened by the addition of neoadjuvant therapy, we need to ensure these patients receive adequate nutrition.

The options for administering EN support are a nasogastric tube (NG), surgical jejunostomy, or the placement of an oesophageal stent. Each option has its advantages and disadvantages. Nasogastric tubes cause discomfort, and increase the risk for aspiration pneumonia in patients who are already at high risk. Surgical jejunostomy is probably the best way to deliver EN, but the procedure requires general anaesthesia, and there is a risk of complications related to the tube or the surgery. Stenting improves dysphagia, but has no effect on cancer-induced anorexia and there is a risk for tumour perforation. Percutaneous endoscopic gastrostomy (PEG) or radiological (PRG) is a more comfortable option, which is also less invasive than the alternative procedures.

However, there are some limitations, particularly with respect to PEG: it can be difficult to get past an obstructive tumour, the colon or liver may be damaged during the procedure and there is a risk of metastatic inoculation at the exit site of the gastrostomy \[^{106}\]. Rarely, there may also be some gastric pull up, and the procedure requires GA \[^{107}\].

PRG may be a more preferable approach compared to PEG. A number of studies involving significant numbers of patients have been carried out, mostly in head and neck cancer patients. The success rates are high (99% to 100%), morbidity rates are low (1.3% to 5.9%) and mortality is less than 1%.

We have recently published our experience of carrying out PRG in oesophageal cancer patients over the period 2002 to 2011 \[^{108}\]. In this retrospective study, we evaluated PRG among unselected oesophageal cancer patients undergoing multimodal therapy, which may, or may not, have included surgery. We looked at the feasibility of using PRG and the procedure-related morbidity. There was also an evaluation of the impact of PRG on the surgical reconstruction after oesophageal cancer resection itself.
In our institution, the PRG procedure is carried out using local anaesthesia with barium enema to delineate the colon and gastric insufflation via an NG tube to avoid injury to proximal organs at the time of gastric puncture. Gastropexy is carried out using three anchorage devices and, for each puncture, there is opacification under fluoroscopic control.

In this study, we looked at records for 1,205 patients, 269 with PRG and 936 without [108]. A total of 517 patients were excluded, as they were not eligible for surgery, were found to be unresectable or did not have reconstruction using the stomach. The remaining 78 patients who received PRG were matched with 156 randomly selected controls without PRG.

The success rate was high: PRG placement was feasible in 96.3% of patients, and sixty-day PRG-related morbidity rates were comparable. Despite a higher malnutrition rate at presentation in the PRG group, overall morbidity, and morbidity related to oesophageal surgery, were similar between the two groups. The median number of attempts at placement was 1 (mean = 1.2). Failure, where it happened, was related to complete obstruction (8) or interposition of another organ (2). Complications led to eight re-operations, five soon after the initial PRG procedure: peritonitis (3), ileal transfixion (1) and haemoperitoneum (1). Post-operatively there was no difference between the groups.

Based on this large study, we believe that PRG is feasible, safe, and has a low associated morbidity. There are no negative effects on outcomes for patients undergoing oesophagectomy with gastric pull-up. PRG also has a positive effect on post-operative outcomes.

3.2 **Nutritional supplementation associated with trimodality therapy: What is the best approach to enteric nutrition support?**

**AGAINST THE MOTION:**

**Donald Low**

**Virginia Mason Medical Center, Seattle, USA**

Although up to 80% of patients with oesophageal cancer are malnourished at the time of diagnosis [109], this is not necessarily associated with an increase in complications; but a decreased overall 5 year survival has been observed [110].

Looking at the evidence for feeding malnourished patients, NCCN guidelines recommend a multidisciplinary evaluation and nutritional assessment, but placement of a PEG is not recommended [111].

There are many advantages and disadvantages associated with any type of EN option, but one of the main problems with gastrostomy concerns the viability of the gut. In a 5-year retrospective review, Keung et al (2012) reported major procedural-related outcomes in 10.6% of 189
gastrostomy patients who underwent PEG placement, and ultimately, the majority of patients failed to achieve total independence of parenteral nutrition \[^{112}\].

Locher et al (2011) were less clear in their review of PEG placement in head and neck cancer patients, concluding that more research was necessary to inform physician behaviour on whether prophylactic PEG placement was appropriate \[^{113}\].

On the other hand, Tessier et al (2013) concluded that tube feeding was feasible and safe in gastrostomy patients \[^{114}\]. However, although mortality was zero and morbidity very low, it was not possible to replicate the results of this study carried out by a highly trained team using radiologically guided tubes.

There are reported cases where a PEG tube has been placed into the body of the stomach prior to chemoradiation, but the location of the PEG tube has affected the blood supply needed to construct the gastric tube which replaces the oesophagus. This can produce an area of necrosis across the top of the gastric tube a few days after the initial operation, with the high suspicion that the PEG tube plays a role. It is always important, when nutritional options are being considered prior to neoadjuvant therapy, to involve the surgeon in decision-making.

In our institution, we routinely use jejunostomy. If jejunostomy is an option, it is carried out as the same procedure as the Portacath and diagnostic laparoscopy. As most patients go back to their own institutions for chemotherapy, we ensure that they have their jejunostomy in place prior to neoadjuvant chemotherapy. Discussion of nutritional status is now a standard part of tumour board discussions. In a review of our previous 245 jejunostomies, the incidence of non-serious complications was 7.3% (18 patients). The most common complication was premature tube displacement.

We have developed post-operative assessments and procedures as part of our enhanced recovery pathways. On day 3, we use post-operative contrast studies to assess gastric emptying with the potential for removing an NG tube immediately. Low volume EN is started on day 1, and baseline medications can be applied through the tube on day 2, and no attempt is made to initiate solid food while the patient is in hospital. We aim for discharge within 7 days, and achieve this in 63% of patients.

In conclusion, patients who require EN prior to neoadjuvant therapy can use the same feeding system that is used post-operatively. Guaranteeing EN helps to achieve the goals of standardised pathways. Surgical insertion of a feeding jejunostomy can be carried out safely with minimal complications, and can typically be done in association with other necessary pre-operative procedures. Feeding tubes inserted within this framework can improve treatment tolerance and are cost-effective.
3.3 Oesophageal cancer: Neoadjuvant stenting

FOR THE MOTION:

Johannes Zacherl
Herz-Jesu Krankenhaus, Vienna, Austria

To counter malnutrition in patients undergoing complex gastrointestinal (GI) operations, especially those in the upper GI tract, it is recommended that nutritional support be given via the GI tract. After reviewing the notes of 58 patients who had undergone neoadjuvant chemoradiotherapy prior to surgery, Bower and Martin concluded that the placement of a removable silicone oesophageal stent was a better option than insertion of a feeding tube [115].

The beneficial effects of neoadjuvant treatment have been demonstrated in a number of recent RCTs, all of which report good overall survival rates, ranging from 3 to 5 years [116-120].

There are a number of options for nutritional access in order to bridge the patient from surgery to discharge. However, only one of these, insertion of a stent, can also relieve dysphagia [121]. Although stents may be subject to dislocation or obstruction after two or three months, this may be all that is needed to cover the period of neoadjuvant treatment. As well as their functional role, stents can also enhance quality of life in the palliative setting in patients with inoperable oesophageal cancer [122].

While stents have been used for a long period in the palliative setting, recent studies have investigated the use of oesophageal stents to re-establish oesophageal patency in patients undergoing neoadjuvant therapy for locally advanced oesophageal cancer. Publications on neoadjuvant stenting have involved only small numbers of patients, just over 200 in total [123-129]. Overall, studies report a reduction in dysphagia following stent insertion, and restoration of swallowing. A problem often reflected in the literature is that of stent migration, usually as a consequence of tumour shrinkage. Migration is usually asymptomatic, has no impact on mortality and rarely causes pain.

One study found that removable, fully covered, self-expanding metal stents in these patients resulted in significant improvement in dysphagia scores [125]. A comparative study by Bower et al (2009) found that, in comparison to patients with feeding tubes or no nutritional support, patients with stents experienced a lower degree of weight loss, mean albumin and lower mortality [124].

In 2009, Siddiqui et al compared stenting with jejunostomy tubes during neoadjuvant chemoradiation in patients with oesophageal cancer [125]. Restoration of albumin was achieved in both groups, but the dysphagia score was lower in the stent group, while those in the jejunostomy group experienced serious complications of about 10%.

A prospective cohort review on gastrostomy tube insertion in 172 patients with head and neck cancer, found that procedure-related
mortality following radiologically inserted gastrostomy (RIG) was higher than those in mixed patient populations \cite{130}. Mortality rates in the RIG group were higher than those with PEG placement. In the systematic review and meta-analysis of 2,379 head and neck cancer patients, the authors found fatality rates of 2.2% following PEG and 1.8% following RIG \cite{130}. The reasons for the post-operative gastrostomy deaths were mainly post-operative peritonitis, intestinal haemorrhage and aspiration pneumonia, which occurred even when the tubes were placed radiologically.

In conclusion, neoadjuvant stenting can increase the patient’s QoL, restore swallowing, stop weight loss and stabilise albumin. Stenting causes no harm to the stomach and no delay to neoadjuvant treatment. It is a trans-oral procedure, reversible, safe, food tolerant and is an established palliation procedure in patients not undergoing resection.

3.4 Self-expanding covered metallic stents as a bridge to surgery: Impact on oncological outcomes

AGAINST THE MOTION:

Christophe Mariette
University Hospital Claude Huriez, Lille, France

Self-expanding metallic stents (SEMS), plastic or metal, have become established in the palliation of dysphagia in unresectable oesophageal cancer \cite{131}. Recently, there have been a number of publications that suggest their use could be extended to include dysphagic patients awaiting resection and those who could benefit from neoadjuvant treatment before resection \cite{126, 128, 129, 132}.

However, in these studies, the rate of complete resection was very low for patients in the neoadjuvant phase, and data on long-term follow up are also very scarce. Although there have been some reported advantages with the use of stents in this type of patient, including immediate relief of dysphagia and the maintenance of oral nutrition, little, if anything, is known about the outcomes.

We therefore carried out a study which aimed to evaluate the impact of SEMS insertion on long-term oncological outcomes before curative oesophageal cancer surgery. The primary objective was to assess 3-year overall survival; secondary objectives were to assess the R0 resection rate, the time to recurrence and 3-year loco-regional recurrence rate.

Thirty French speaking European centres were involved, recruiting all consecutive adult patients undergoing surgical resection for oesophageal cancer. A total of 2,944 patients underwent surgery. Each patient who received pre-operative stent insertion (38, SEMS group) was matched with four control patients (total 152). There was a good match of all demographic and tumour factors at baseline \cite{133}.

In the SEMS group, there were two oesophageal perforations, chest pains in five patients and five cases of dysphagia. Following surgery,
there was no difference in 90-day complications, in-hospital post-operative mortality, anastomotic leakage, surgical site infection and major morbidity. However, the presence of a stent impaired surgical resection, limited the radicality of the surgery and increased the risk of positive circumferential margin.

Median survival was significantly better in the non-SEMS group (27.5 vs 17.4 months, p=0.20) along with median time to recurrence (9.0 vs 6.5 months, p=0.042) and 3-year loco-regional recurrence (47.9% vs 65.7%, p=0.041).

Taking all of these results into consideration, the presence of a SEM was an independent predictor of poor prognosis, following adjustment for possible confounding factors. It was also an independent predictor of incomplete resection. The results were not changed by exclusion of the two cases of SEMS-related perforation.

These results are in line with other published studies, suggesting that placement of a SEM can increase the risk of tumour cell dissemination [134] and reduce overall survival [135].

In conclusion, SEMS placement before surgery for oesophageal cancer impacts negatively on oncological outcomes with significantly lower RO resection rates, time to recurrence and overall survival and higher rates of loco-regional recurrence.
PART 4: PERI-OPERATIVE OPTIMISATION

Chairs:
Shaun Preston (UK)
Donald Low (USA)

4.1 Haemodynamic management: OPTIMISE trial

Rupert Pearse
Professor of Intensive Care Medicine
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It has been difficult to draw conclusions about the benefits or disadvantages of haemodynamic therapy due to the large number of conflicting publications and reviews on the subject. In 2013, Grocott et al produced a Cochrane systematic review which assessed all the current analytic approaches, coming to the conclusion that there is some evidence that haemodynamic therapy reduces complications, but the evidence is not strong for an effect on mortality $^{[136]}$. A major problem with haemodynamic optimisation to date has been the quality of research. Most studies use a small sample size, objective outcome measures are not employed and are interpreted variably, complications are assessed in an unblinded fashion, and the care of control groups is sub-optimal.

A large clinical trial, “OPTIMISE” (OPTimisation of cardiovascular Management to Improve Surgical outcome), sets out to answer the question: does a haemodynamic therapy algorithm guided by cardiac output monitoring decrease the number of patients who develop complications within 30 days of major GI surgery?

The study included high risk patients to ensure a significant event rate, while patients with acute MI, pulmonary oedema, septic shock and so on were excluded. It is a multi-centre trial in 16 UK centres, including 734 patients (367 in each arm) with a 90% power to detect a 25% reduction in death rate or a drop in moderate/severe complications from 50% to 37.5% within 30 days.

The haemodynamic therapy algorithm begins with general measures, such as the maintenance of haemoglobin; a green coloured box outlines the fluid therapy, a blue box covers the use of dopexamine and a final box deals with the possibility of additional blood or IV fluid.

The primary outcome measure includes a long list of complications that may be produced, or exacerbated, by the therapy. The secondary outcome measures include seven-day post-operative morbidity, 30-day mortality, infectious complications and critical care days, hospital length of stay and 180-day mortality.

Recruitment has already been completed, with a delay of only 3 months compared to target. In total, 1,735 patients have been screened and 1,001 excluded, the most common reason being that the patient declined or that no research staff were available.
The baseline data show that few non-elective patients have been included so far and there is a slightly higher incidence of renal impairment in the intervention group. There has been over 90% compliance with the protocol in both arms of the trial and, in at least 94% of cases, the assessor felt that they were truly blinded to the allocation.

Similar volumes of fluid were given in the two groups, although colloids rather than crystalloids were more commonly given in the intervention group. The intervention group were given slightly less fluid before surgery but more afterwards, possibly due to the fact that this group were being supervised for 6 hours following surgery.

During the peri-operative period, the majority of patients were given a bolus of a vasoactive drug, and the critical care admission rate in both groups was the same at around 80%.

The results are not yet published, so can only be described here in general terms. The primary outcome, complications or death within 30 days, was higher in the standard care arm than in the haemodynamic therapy arm, and there was a similar pattern in the long-term outcomes, with event rates being higher in the standard care group.

Regarding 180 day survival, there was a slightly higher rate of mortality in the intervention group early on, but there is a better mortality rate in the intervention after 30 days, highlighting the importance of long-term follow up beyond 30 days.

In the secondary outcomes, the most striking difference was a lower rate of infections in the intervention group. A sub-group analysis suggested that, if the group had not included emergency surgery patients, the overall outcome would have been significant.

Some patients in the intervention group had a serious cardiovascular event at 24 hours, compared to none in the usual care arm, but by 30 days the event rate was the same. One suggestion is that the event rate could have been influenced by dopexamine rather than fluid.

Overall, haemodynamic therapy led to no significant reduction in the primary outcome. This lack of difference may relate to a lack of statistical power, and perhaps there is still a need for a larger trial. However, clinical practice should be re-evaluated regardless of the fact that the data were not significant.

### 4.2 Haemodynamic management in the immediate post-operative period following oesophagectomy: Advantage of standardised pathways

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Over the past 20 years, the make-up of patients presenting at our institution has been changing; the mean age has increased, mean BMI has risen, the incidence of diabetes has increased, and patients in clinical stage III is on the rise. Taken as a whole, the patients we see are becoming more complex.
By contrast, over the same period, operative blood loss has come down, use of operative fluids has reduced, ICU stay and hospital stay is shorter, and hospital mortality rates have remained under 1%. In 2003, we reported that intra-operative fluid restriction appeared to result in better outcomes \[^{137}\]. 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. 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.

Following oesophageal resection, the point of greatest vulnerability is the gastric graft. In 2013, Page et al reported on the use of routine endoscopy to assess gastric mucosal ischaemia and detect anastomotic leakage \[^{138}\]. One hundred consecutive oesophagectomy patients were examined in the first week following surgery. On examination, 15 patients showed gastric mucosal ischaemia, two had anastomotic leaks, and four showed ischaemia plus leakage. There was no evidence that the endoscopy caused damage to the anastomosis or gastric conduit. It was clear that mucosal ischaemia is much more common than had previously been recognised, and the graft is at risk in every operation.

Protocols and standardised clinical pathways, dictating how the patient will be managed in the peri-operative period, can be employed to minimise the risk of ischaemia. At Virginia Mason Medical Center, we adopt a conservative approach to the use of intra-operative fluids, regional rather than general anaesthesia, we avoid peri-operative transfusion, and aim for early mobilisation \[^{137}\].

At VMMC, 58% of patients presenting for oesophageal resection have undergone neoadjuvant chemotherapy, 30% present with HCT<30, but we do not transfuse unless HCT drops below 25 for two consecutive days.

Another pathway covers the use of anaesthesia from the pre-anaesthesia induction room, through intra-operative to post-operative pain management. A mainstay is thoracic epidural which has documented benefits \[^{137}\]. Many surgeons believe epidurals to be time-consuming and unreliable. However, in our view, they 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.

Reported morbidity and mortality rates following oesophageal resection after neoadjuvant chemotherapy can be very high, with one-third of patients being ventilated overnight \[^{139}\]. 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 \[^{140}\].
These current protocols minimise the risk factors for conduit ischaemia. Gastric conduit perfusion is dependent on good microcirculation, the maintenance of venous drainage and baseline arterial perfusion pressure. An extensive sympathetic block does have the capacity to induce mesenteric dilation, decrease arterial pressure and affect splanchnic blood flow in vulnerable areas. Two trials are important in directing how we manage haemodynamics in the immediate post-operative period [141, 142].

In a study by Al-Rawi et al (2008), ten patients were given intravenous adrenaline following intra-operative epidural bupivacaine during oesophagectomy [141]. Laser Doppler flow probes were sutured to the stomach near the pylorus and tip of the gastric conduit near the anastomosis. While gastric flux was significantly decreased by the bupivacaine, it was restored to baseline by the adrenaline infusion. Klijn et al (2010) confirmed that the use of vasopressors has no detrimental effects on conduit microvascular blood flow [142].

These parameters are now routine in the VMMC protocol for anaesthesia; the rate of epidural is adjusted according to patient pain. If mean arterial pressure falls below 70 mmHg, the patient will receive a 500 cm³ bolus over 60 to 90 minutes, with the possibility of a second bolus over 4 to 6 hours, followed by a surgical staff review. If hypotension persists, we will initiate a phenylephrine drip.

The contemporary approach to oesophagectomy matches the operation to the patient’s physiology and cancer presentation. The process should be kept as simple as possible with no central venous lines, the expectation of minimal blood loss, effective communication with anaesthesia and a step-down or specialist unit rather than ICU.

In conclusion, standardised protocols must be built into order-sets to maintain peri-operative mean arterial pressure and to maintain graft perfusion.
PART 5: SURGICAL OUTCOMES IMPROVEMENT INITIATIVES AND PRACTICE SHARING

Chairs:
Christophe Mariette (France)
Robert Martindale (USA)

5.1 EURECCA European project

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EUROCaRE 5 data reported last year, providing regional age-specific five-year relative survival rates for gastric cancer diagnosed between 2000 and 2007. There are significant regional variations with approximately 15% to 20% greater survival for all ages between Southern Europe and the UK and Ireland. Between 1999 and 2007, there has been very little improvement, despite restructuring of cancer services and introduction of multidisciplinary treatments.

EURECCA, the European Registration of Cancer Care, is a Europe-wide initiative to collect data on the management of cancer across Europe. Its aim is to establish a database for a European Upper GI audit that is consistent across all countries, in order to investigate these differences in outcomes. Some countries, such as the Netherlands, England, Sweden and Denmark, have centralised specialist services, while others, such as Italy, Germany, Spain and Poland, have a range of large collaborative groups and smaller local services.

The first step has been to set up a common dataset based on existing national registries and audits. Datasets were examined for variation in the data items. There was a range of 40 to 650 items capturing patient characteristics, comorbidities, staging, diagnostics, non-surgical treatment, neoadjuvant treatment, surgery, post-operative course and complications, pathology, survival and follow up.

The datasets were compared with regard to the type of data collected, for example, categorical, number, present or absent, free text. Forty-five data items were consistent across all the countries that submitted information, and these formed the basis of a dataset proposed to compare outcomes across countries.

The first results were presented by each of the participating countries (the Netherlands, UK, France, Spain, Ireland, Germany and Denmark) in 2013 at the 10th International Gastric Cancer Congress. Information on nearly 4,000 oesophageal and just over 2,000 stomach cancers treated in 2011 to 2012 was available. Approaches to neoadjuvant treatment and surgery, as well as post-operative mortality were described.

There is variation in the use of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy in oesophageal cancer. The use of
neoadjuvant chemotherapy in stomach cancer shows some variation, but is less marked than in oesophageal cancer.

There are also differences in the surgical approach to oesophageal cancer, with surgeons in some countries preferring trans-thoracic procedures, while in others, there is a greater proportion of transhiatal, although across all countries trans-thoracic approaches predominate. In gastric cancer, there are variations in the proportion of total gastric resections in comparison to distal gastrectomy, which mainly reflect known differences in epidemiology between the countries.

Operative mortality rates, including 30 day and in-hospital deaths, are broadly similar for both oesophagectomy and gastrectomy.

These findings raise a number of questions. Are there any other data items which should be included? Are complications defined in the same way? Are there any differences in the outcome indicators and in pathology reporting? Could any of the differences between countries be accounted for by differences in disease staging at the time of diagnosis, by treatment protocols, by the proportion of curative surgery or multi-modal treatment?

Development of the EURECCA registry is planned to address these questions by including data from more countries and more detailed information to low comparison of post-operative outcomes, resection rates, patterns of care and long-term outcomes. This is a huge task but the information will be valuable to all institutions across Europe.

5.2 International initiative: ISOS - International Surgical Outcomes Study

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The volume of surgery worldwide is not accurately known, but estimates have suggested around 234 million procedures take place every year [143]. There is also a lack of information about the true mortality rate of surgical procedures. However, even conservative assumptions suggest that there are large numbers of avoidable deaths each year.

Evidence suggests that most deaths are associated with a high risk surgical population, with over 80% of the deaths being accounted for by 12.5% of the surgical population [144]. Unfortunately, it is not always easy to identify these patients. Cardiac surgery provides a good example, where high risk patients are routinely identified, with the result that mortality in this area is reducing year on year.

In a study on north American hospitals carried out through 2005 to 2007, risk-adjusted mortality rates for similar surgical procedures varied from 3.5% to 6.9%, while overall complication rates were 24.6% to 26.9% respectively [2]. However, the mortality of patients experiencing major complications was twice as high in those hospitals, with very high overall mortality (p<0.001) suggesting that the severity of complications may be related to how these patients are managed [2].
Medicare data from the US on over 60,000 patients, found that the incidence of adverse events declined substantially from 2005 to 2011 among patients hospitalised for acute MI or congestive heart failure, but not in those hospitalised for pneumonia or conditions requiring surgery [145].

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, and ultimately reduce the number of preventable deaths. In the EuSOS study, there was wide international variation in the adjusted mortality risk, but the confidence intervals were very wide (see Figure 11). 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 [146].

We need a study in this area as we have a very poor understanding of the overall surgical population, and how complications relate to death rates. The study design of the International Surgical Outcomes Study (ISOS) is highly pragmatic, being an observational 7-day cohort study, with the patient followed up until hospital discharge. Data collection is by website entry of anonymous data.

The primary objective is the incidence of in-hospital complications, while secondary objectives are the in-hospital mortality associated with complications, the relationship between complications and the use of critical care, and the effect of complications on duration of hospital stay.

All adult patients who are undergoing elective in-patient surgery during the 7-day study period of April, May and June 2014 are eligible for inclusion. Patients undergoing emergency surgery, radiological procedures or with a planned overnight hospital stay are excluded. Data is collected on all eligible patients during the one week period and includes baseline data and follow-up for a maximum of 30 days. Only hospitals with 20 valid patients will be included, to avoid distortion of the data.

Once completed, the data from this important study will be made publicly available for research and audit.

5.3 UK Enhanced Recovery Initiative in Upper GI surgery

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The importance of enhanced recovery programmes has been recognised in many types of surgery, including hip, knee, hysterectomy and prostatectomy, resulting in a total of 70,000 fewer bed days per
year in the UK (see Figure 12, NHS England data). However, there has been no improvement in other areas, such as surgery of the oesophagus, stomach, liver and pancreas. Even within established practices, significant variations exist between, and within, regions.

The Enhanced Recovery Partnership has been set up to encourage work in developing specialities. Four institutions, which are currently working to implement ERAS principles in their institutions, provided data on their programmes to the 2012 Enhanced Recovery Summit.

Nottingham City Hospital introduced an ERAS pathway in 2009 for oesophageal and gastric cancer resections, which resulted in a reduction in median LOS of five days. As part of the process, a greater percentage of laparoscopic procedures were performed. There was no change in mortality or in the overall complication rate, but, within this data, there was a drop in minor complications with an increase in major complications, the reasons for which are not yet clear.

The Royal Marsden NHS Foundation Trust introduced ERAS protocols for oesophagectomy and gastrectomy in 2010. An audit of the results found a four day reduction in median LOS for oesophageal resection and a three day reduction for all types of gastrectomy.

At the Royal Surrey County Hospital (RSCH), a review of 144 patients, before and after the introduction of an ERAS protocol for oesophagectomy, showed that demand for the most expensive critical care beds at level 3 fell after introduction of the pathway. This was balanced by a slightly longer stay of patients in level 2, and a small reduction in the need for level 1 beds [147].

The audit was also able to reveal differences in individual surgeon data: the surgeon who adopted the ERAS protocol in full saw a six day reduction in median LOS, while colleagues who adopted only part of the pathway saw a smaller three day reduction in median LOS.

At Newcastle upon Tyne NHS Foundation Trust, there was a reduction in median LOS of four days, and a reduction in the severity of complications following oesophagectomy.

A comparison of the costs of care, before and after introduction of the pathway, at RSCH for oesophagectomy showed that, initially, the cost per patient increased, but once the pathway became a routine part of practice, approximately £5,000 could be saved per patient.

At Nottingham there was a saving of approximately £3,500 per patient for a combination of oesophageal and gastric resections. Gastric
surgery is a less expensive procedure, which may explain why the overall savings appear less than at RSCH, but individual savings of this magnitude can produce an annual saving of over £300,000 per unit. We are seeing progress in the adoption of ER protocols throughout England. NHS England have stated that enhanced recovery should now be considered “standard practice for most patients undergoing major surgery”, an aspiration that is supported by the heads of most of the major professional societies. The National Enhanced Recovery Advisory Board aims to take forward adoption of these principles in areas where LOS has not seen any change, such as in surgery of the liver, lung, upper GI, breast reconstruction, pancreas and in Caesarean sections. This practice is likely to influence commissioning of services in the future, and is, therefore, crucial for most institutions. In the future, purchasers may commission services only at hospitals where best practice in this area has been adopted.

5.4 Enhanced Recovery After Surgery (ERAS): An ongoing revolution?

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It is easy to focus on new techniques when considering what improvements can be made to the surgical process. But equal attention needs to be paid to improving surgical outcomes. Post-operative complications increase the length of stay, delay treatment, increase cost and reduce prognosis and quality of life.

Following surgery, the goal of recovery is to restore normal GI function, control pain and nausea, minimise complications and restore mobility. The ERAS protocol is an evidence-based means of achieving these goals [40]. It is a multi-modal and multi-disciplinary way of working, emphasising the involvement of the full team, especially the surgeon and anaesthetist, as many factors in the protocol are under their direct control. The elements of the ERAS approach have already been discussed in detail, but it is important to stress that the results should always be audited.

The historical approach to surgery, involving bowel preparation, starvation, sedation and post-operative bed rest and fluid overload, can be compared to the more physiological ERAS approach, which leads to reduced surgical stress and improved insulin sensitivity [34].

Many studies have debunked the dogma of surgical practice. Muller et al (2009) reported on the application of fluid restriction and effective epidural analgesia in a group of patients undergoing colonic resection [148]. Compared to a control group, the fast track group experienced a significant reduction in general and surgical complications and length of hospital stay. Other studies have also shown a direct relationship between fluid overload and post-operative complications (see Figure 13) [149].
A systematic review of the practice of bowel preparation involving 14 RCTs and nearly 5,000 patients found no benefit in the practice, with no difference in leaks or infection \[150\]. In fact, the rate of surgical site infections was better without bowel preparation.

Another systematic review found that the use of gastric tubes was associated with more complications and a longer length of stay \[151\], while a review of the use of prophylactic drains in colorectal surgery found no benefit in their use in hepatic, colonic or most cases of rectal resection \[152\]. A later review confirmed that surgery was safe without drainage, that there was no reduction in complications with a drain and that, in fact, the use of drains might increase the complication rate \[153\].

A review of outcomes in 2011 found the best documented outcomes in colorectal surgery, in which the complication rate was reduced by 50% and hospital stay by about three days \[41\]. Also in 2011, Gustafsson et al demonstrated that improved adherence to ERAS led to an improved post-operative outcome (see Figure 14) \[154\].

Despite the documented benefits of adopting an ERAS approach to surgery, only 40% of surveyed colorectal specialists were found to have an ERAS protocol in place. More worrying was that only 1% could supply ERAS data and discuss the outcomes.

Without rigorous audit of procedures, units may think they are adhering to ERAS principles whereas, in reality, they may only be complying with a fraction of the recommendations. An audit of the elements of ERAS in CHUV and 11 hospitals in Lausanne found that improved compliance led to a steady reduction between 2011 and 2013 of important factors such as length of stay. New surgical procedures are being added step by step.

Quite apart from the clinical benefits, it can be demonstrated that ERAS is a cost-effective approach to surgery. In a prospective audit of...
the use of the protocol in colorectal surgery, the major complication rate reduced from 22% to 12%, hospital stay was down from 10 to 7 days and the cost per patient was reduced by 1981CHF [155].

In summary, ERAS reduces complications and hospital stay. It is vital to continue to check on compliance and to avoid creating new dogmas to replace the old ones.

5.5 Stepwise enhanced recovery implementation in Upper GI: Initial experience in a Russian centre

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Enhanced Recovery After Surgery is acknowledged to be a standardised application of evidence-based practice to peri-operative care. The main components are pre-operative patient evaluation and optimisation, intra-operative control of blood loss and infusion rate and post-operative pain control, mobilisation and nutrition.

Although ERAS has been implemented successfully in many western countries, it is not clear that the same experience can be easily translated outside of the major international institutions. In Russia, the majority of surgery takes place in non-specialist and non-academic centres, and ERAS programmes may need significant adjustment if they are to be incorporated into these healthcare systems.

In Russia, there are major structural barriers to making changes in the patterns of care. Most patients receive their care via public insurance programmes, under which payment is made per patient. However, hospitals involved in these programmes receive a budget which is related directly to the number of beds, not to the number of cases. There is, therefore, little economic motivation to implement ERAS protocols in these institutions as there will be no financial support for additional patients that can be treated under these pathways.

For complex surgery, carried out in high-volume centres, payment is per case and there is, therefore, good motivation to implement ERAS pathways. However, not all major centres participate in the programme. There is also a high probability that economic situations will not allow continuance of the programme beyond 2014.

In addition to economic disincentives, there are challenges concerning education of staff; the mean level of education amongst staff is quite low, with no formal continuing medical education programmes available. The patient mix is also very challenging, with a huge proportion of cancer patients presenting in the most advanced stages.

Staff education has been valuable in developing motivation, even in the face of systemic barriers. There has been a necessity to educate surgeons, intensivists, as well as many nurses abroad, to establish a common language and a unified approach to peri-operative care. A new and very young team has been brought together in visceral surgery, the members of which are keen to make a difference to patterns of care. ERAS components have been implemented in upper
GI: pre-operatively, there is no bowel preparation, fasting or premedication; intra-operatively epidural analgesia is used, nasogastric tubes are avoided, and there is limited fluid administration; post-operatively, there is early mobilisation and enteral or oral nutrition.

In conclusion, it is difficult to implement ERAS pathways in developing countries. It is essential to have a team in place, and a major task is the development of logistics to support enhanced recovery. Constant education is a significant requirement for the entire team, including research nurses, ERAS nurses, nutritionists and so on. We have also learned that a step by step approach is necessary to reach our goals.

In the future, our goals are to audit our progress, feedback to the clinical team and to extend the development of enhanced recovery pathways to other specialities.

5.6 Practical approach to introducing ERAS clinical pathways in Upper GI surgery

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In June 2012, an ERAS clinical pathway for upper GI surgical patients was introduced in our institution. In the 18 months since then, 84 patients have gone through the pathway undergoing oesophagogastrectomy with oesophagogastric resection with oesophagogastric or oesophagocoloplasty (18) or intrathoracic oesophagojejunoplasty (22) were excluded from this evaluation.

Our audit of these patients revealed varying levels of compliance with the single ERAS items. There was 100% compliance with pre-operative risk assessment. All patients were encouraged to give up smoking and to practice pre-operative inspiratory muscle training, which has been shown to improve pulmonary function [156 - 159].

All patients received counselling. It is difficult to assess the effectiveness of this intervention without patient feedback, but the literature suggests that good counselling is a predictor of success in ERAS [160, 161]. Due to the lack of evidence in this area, we have produced a booklet for patients explaining the procedures and have started a prospective study to compare the response of patients with, and without, the booklet.

Pre-operative carbohydrate loading was given to 90.5% of patients. Those that did not receive carbohydrate loading tended to be seen in the early days after the introduction of ERAS and later there were some oversights from new members of the team. No studies have assessed the effectiveness of carbohydrate loading in oesophagectomy, but it seemed worthwhile to assess the effect of carbohydrate loading in upper GI patients in light of the good results reported in large bowel surgery.

Only 87% of patients received pre-operative immunonutrition. The reasons for not receiving immunonutrition were practical: it was difficult to find the product in the region (Lombardy), where it is not...
recognised as a free prescription product. Moreover, some patients rejected it as unpalatable (efforts to market other tastes such as tropical fruits in Italy would be welcomed by patients). Published evidence reports that patients with oesophageal cancer are prone to malnutrition, which probably affects outcome, so it seems even more important for these patients to receive pre-operative immunonutrition [162-166].

In the literature, thoracic epidural analgesia (TEA) is regarded as the gold standard for open oesophagectomy, providing better pain relief than systemic opioids. In our review, 83% of patients received TEA. Reasons for not applying TEA were refusal by the patient, clinical reasons and technical difficulties. It has still to be demonstrated if the intra-operative use of TEA can cause hypotension.

Only 22.6% of patients received pre-operative corticosteroids, however, this item has only recently been introduced to the protocol. Use of pre-operative corticosteroids has recently been reported to reduce complications and LOS following major abdominal surgery [167].

We used goal-directed fluid therapy in 76% of patients, monitoring haemodynamic parameters such as cardiac output, stroke volume and stroke volume variation with Vigileo®, along with haemogasanalysis and urine output. Prior to June 2012, use of Vigileo was random. This is a difficult area, as no consensus exists regarding peri-operative fluid therapy and the different regimens and end points used in the studies make it difficult to draw conclusions [149, 168-172].

The vast majority of patients, 96.4%, had early extubation, a practice which is widely supported in the literature [173]. It has been reported that prophylactic overnight mechanical ventilation contributes to pulmonary morbidity, with higher rates of ventilator-associated pneumonias, barotrauma and acute respiratory distress syndrome.

Most patients, 87%, were sent to floor, mostly for prophylactic monitoring of very high risk patients, surgery that ended late in the day, patients with extensive upper mediastinal or neck dissection for lymphadenectomy at risk of recurrent injury with consequent aspiration.

Two-thirds of patients received enteral feeding, and 54% started this very early, on post-operative day 1 through jejunostomy. Gastric tube removal took place in 89.3% of patients, mainly on day 3, 90% within four days. In some patients, the tube needed repositioning, and there were a few cases of fistula and bilious emesis. Oral feeding was started in 62% of patients within four days.

Complications were classified according to CD criteria. There were 11 anastomotic complications, including five fistula, 22 respiratory complications, 16 of which were mild, five transient and two severe neurological complications. Other complications included a massive haemorrhage in one patient. Globally, in-hospital mortality was 2.4% and two patients were re-hospitalised within 30 days, mainly for nutritional problems.

The goal was to discharge patients by day 9, and this took place in 68% of patients.
To conclude, in the period immediately following introduction of a protocol, it is very hard to achieve 100% compliance with all the elements, despite the best efforts of the team. A stepwise approach is needed. Applications of standardised clinical pathways might reduce complications in patients at low and moderate risk. In higher risk patients, minor complications are reduced but to a lesser extent. Intra-operative anaesthesia is crucial. Over 60% of patients following the pathway were able to be discharged early, 73% had no or only minor complications, while the remainder had major complications that may require technical modifications or variation of the protocol.
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