**Immunonutrition and surgery**

Understanding of the clinical and health economic value of immunonutrition for different types of surgical patients has continued to advance since the publication of the 2006 ESPEN guidelines on the role of immunonutrition in surgery. In this Symposium, speakers provided an overview of all guidelines regarding immunonutrition, including those by ERAS, a review of the evidence concerning the use of immunonutrition in GI cancer surgery; and the results of a recent randomised controlled trial on the role of immunonutrition in minimally invasive surgery for resectable oesophageal cancer.

Chairmen: Christophe Mariette, MD, PhD – France; Nicolas Demartines, MD, FRCS, FACS – Switzerland

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**Immunonutrition in the ERAS guidelines and other surgery guidelines**

Since 2011, there have been 10 systematic reviews on the subject of immunonutrition. The body of evidence upon which these reviews are based consists of a total of about 17 RCTs investigating pre-operative immunonutrition.

In 2006 a very influential paper, the ESPEN Guidelines on enteral nutrition in surgery, including organ transplantation, was published, reaching the conclusion that in cancer patients undergoing major upper abdominal surgery, pre-operative enteral nutrition, preferably with immune-modulating substances, can be recommended for five to seven days, independently of nutritional risk. This was graded A, the highest grade in the Oxford Grading System. The recommendation was based on data from five RCTs in abdominal cancer surgery of which only one was a double-blinded trial, while the other four were unblinded.

Consensus was harder to reach when ERAS began to put together guidelines for Whipple’s procedure and for gastrectomies. After reviewing the evidence the use of immunonutrition was not uniformly recommended, but the authors differed in their interpretation of the evidence.

Cerantola et al (2011) published a meta-analysis that reached conclusions in accordance with the 2006 ESPEN guidelines regarding immunonutrition. This meta-analysis also included data from six double-blinded trials published since 1999. One double-blinded RCT (Lobo 2006), which concluded that there was no clinical advantage arising from the use of immunonutrition was not included in the meta-analysis.

ERAS surgical guidelines are now being updated and the 2012 publication by Gustafsson et al concluded that immunonutrition could be considered in open colonic resections, but that the evidence was weak.

In the same year, an update was published for peri-operative care of patients undergoing pancreaticoduodenectomy. The conclusion was that the balance of evidence suggested that immunonutrition for 5 to 7 days pre-operatively could be considered because it may reduce the prevalence of infectious complications in patients undergoing major open abdominal surgery. But the evidence level was moderate and the recommendation weak.

In 2013, updated guidelines for peri-operative care following radical cystectomy for bladder cancer were published. The conclusion was that, although immunonutrition is clearly indicated for major GI procedures, its role in reducing morbidity and mortality in urology remains unknown. An overview in this area suggested that the role of immunonutrition in bladder cancer should be considered investigational.

The most recent ERAS guidelines were for gastrectomy in which it was concluded that the possible benefit of reduced infectious and wound-healing complications after major GI cancer surgery had not been reproduced in dedicated high-quality trials on gastrectomy patients. A benefit cannot be completely excluded, but there is currently insufficient evidence to recommend routine use in this patient group. The evidence level for this statement was moderate as the data from double-blinded RCTs was either conflicting or showed no benefit.

A trial published in 2013 that supported the use of arginine-supplemented enteral nutrition in gastrectomy patients was considered to be scientifically flawed and was eventually retracted.

The main reason for such a range of different conclusions is probably the selection of data that was included in the systematic reviews and meta-analyses. The gold standard for evaluating cause and effect in medical interventions is the double blind RCT. There are some areas that are not well suited for a randomised study design, particularly skill-dependent interventions with a learning curve, such as laparoscopic versus open resection. In such a situation there would be inadequate blinding, with poor internal and external validity.

Another situation where the RCT is usually inappropriate is the assessment of complex interventions such as the ERAS protocol versus traditional care. Blinding cannot be achieved, there is a significant Hawthorne effect, the control group is generally very poor and is easily contaminated. However, the double-blinded RCT remains the gold standard where it can be performed.

Immunonutrition is a perfect candidate for double-blinded RCT. Blinding is very easy to achieve and complete, it is easy to deliver and requires no learning curve, it is a stable intervention and there is no contamination between groups. For investigations of immunonutrition, the gold standard is well within reach and we should accept nothing less. This implies that we should have meta-analyses that only include double-blinded trials with isonitrogenous control regimens.
Evidence review on immunonutrition in GI cancer surgery

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The Enhanced Recovery After Surgery approach (ERAS)\textsuperscript{17} is made up of several components, such as pre- and post-operative nutrition, pre-operative carbohydrate loading, adequate analgesia, fluid restriction and early mobilisation, as confirmed in prospective studies. However, nutrition is the area that is most likely to be adversely affected by patient compliance, therefore audit is essential.

Poor nutrition is linked to mortality and to complication rate.\textsuperscript{18} Schiesser (2008), among others, pointed out a direct relationship between peri-operative malnutrition and post-operative complications.\textsuperscript{19} In their study, 40% of malnourished patients suffered complications compared to 14% of adequately nourished patients.

Is risk related just to the nutritional component, or do immunomodulating substances also play a role in post-surgical recovery? What is the evidence for factors such as arginine, omega-3 polyunsaturated long-chain fatty acids (PUFAs), RNA and anti-oxidants?\textsuperscript{20}

The evidence has been assessed in a number of reviews including a systematic review in 2010 of high risk surgical patients,\textsuperscript{20} and one in 2011 of peri-operative arginine.\textsuperscript{21} In addition, there have been two investigations into the cost-effectiveness of immunonutrition, one carried out in the USA and one in Switzerland.\textsuperscript{22, 23}

With six meta-analyses and reviews on the role of peri-operative immunonutrition in surgical patients,\textsuperscript{2, 24–28} all reporting a similar reduction in complications, infections and length of stay, it is clear from the evidence that there are benefits to be gained. The data is weak though regarding when it is best to give either standard enteral nutrition or immunonutrition.\textsuperscript{29}

Despite this, some individual studies in major surgery have reported negative results. 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.\textsuperscript{30} This study enrolled a large number of severe cancer patients whose tolerance of nutritional supplements was low and many patients simply did not take an adequate quantity of supplement. These results highlight the importance of patient compliance in the assessment of the benefits or otherwise of immunonutrition in cancer surgery.\textsuperscript{31}

From the payer perspective, the hospital needs to consider the additional cost of immunonutrition against possible reductions in complications and LOS. Assuming compliance is good, specific economic analyses have shown that immunonutrition in this setting can be cost beneficial.

An economic analysis conducted in 2005 on the US national database included 126 US hospitals with around 1 million patients.\textsuperscript{23} 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 for medical patients of over €2000 per patient, even after including the additional cost of nutrition. The cost saving was lower for surgical (€688) and trauma (€308) patients but is still significant when multiplied by the number of these patients.\textsuperscript{23} The net cost savings per patient were particularly significant for upper GI surgery patients (€6300/patient).\textsuperscript{32} The additional cost of immune-modulating formulae were more than offset by savings associated with decreased treatment of complications. Benefits are seen as soon as the infection rate rises above 3.5%.\textsuperscript{32}

Similar results were reported in 2014 by Chevrou-Severac for Swiss patients undergoing GI cancer surgery, where a cost saving per patient of around 1,000 CHF was found if immunonutrition was given post-operatively, rising to over 2,500 CHF if immunonutrition was given pre-operatively.\textsuperscript{33}

**Swiss CE analysis of systematic review**

| Sensitivity analysis Marginal hospital savings per patient thanks to IN used per-operatively |
|-------------------|--------------------------|
| **Baseline infections rate** | **Savings per patient’s stay** |
| **<1%** | **CHF 0** |
| **1%** | **CHF -500** |
| **2%** | **CHF 500** |
| **3%** | **CHF 1,000** |
| **4%** | **CHF 1,500** |
| **5%** | **CHF 2,000** |
| **6%** | **CHF 2,500** |
| **7%** | **CHF 3,000** |
| **8%** | **CHF 3,500** |
| **9%** | **CHF 4,000** |
| **10%** | **CHF 4,500** |

Following implementation of an ERAS programme for colorectal cancer over the period 2011 to 2012, the first 50 patients were compared with the last 50 patients treated before introduction of the ERAS programme. There was a saving of almost 2,000 CHF per patient associated with the ERAS programme, largely due to reductions in complications (20% to 12%) and length of hospital stay (down to 6 days).\textsuperscript{33}

Similar data for surgery of the liver and pancreas during the period 2013 to 2015 is in press, showing that implementation of an ERAS programme can save around €3,500 and €7,700 per pancreas patient respectively. Savings are seen regardless of whether immunonutrition is given pre-operatively or post-operatively.

In conclusion, nutrition and immunonutrition 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 show it is a cost effective intervention.

**Immunonutrition in minimally invasive surgery for resectable oesophageal cancer**

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Most surgery for oesophageal cancer is still carried out with an open abdominal or upper thoracic approach which carry high mortality and morbidity rates. Mortality is 2 to 10%, infectious complications can be as high as 50%, with pulmonary complications responsible for 50% of deaths.\textsuperscript{34}

In retrospective studies on cholecystectomy and reflux surgery, laparoscopic techniques have been shown to decrease post-operative morbidity, due to decreased surgical trauma and less deterioration of the ventilatory mechanisms. A laparoscopic abdominal approach...
may offer several advantages including a lower rate of pulmonary complications, no laparoscopic tumour dissection and greater reproducibility.

We initiated a phase 3 trial (the MIRO trial: Hybrid minimally invasive vs open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised phase III controlled trial) to test the hypothesis that a laparoscopic abdominal approach (laparoscopic gastric mobilisation) could decrease the major post-operative complication rate in surgery for resectable oesophageal cancer. The primary endpoint was 30-day major post-operative morbidity (Clavien Dindo grade II – IV) and the secondary endpoints were 30-day post-operative mortality, 30-day major pulmonary complications, disease-free and overall survival, quality of life and medico-economic analysis. The trial was funded by the French National Cancer Institute.

An important feature of the trial is that many quality controls were included: all centres were supervised by the principal investigator, and received a video and surgical education.

ERAS guidelines on peri-operative care, nutrition and immunonutrition were also followed regarding nutritional support, fluid balance, sedation, ventilation, pain management, extubation and so on. The definition of complications – which can be highly variable – was also standardised: an independent observer carried out a blinded evaluation of the presence and severity of complications which was then reviewed by a medical committee. Data monitoring was carried out for all patients and all reports.

All patients eligible for surgery for oesophageal cancer, any stage, receiving neoadjuvant therapy were eligible for inclusion. Before randomisation all patients received laparoscopic examination of the peritoneal cavity to look for peritoneal tumour deposit or cirrhosis that would contraindicate surgery. In all 219 patients were screened, and 207 were randomised: 103 to the hybrid minimally invasive approach (HMIO) of laparoscopic gastric mobilisation and open thoracic oesophagectomy, and 104 to the open group with open gastric mobilisation and open thoracic oesophagectomy. Analysis was ITT with one patient in each arm excluded. There were no major differences between the groups at baseline in any variable. Of note is that more than 75% of patients received neoadjuvant treatment.

The minimally invasive approach did not increase the risk or length of the surgery which was around 5 hours in both groups. There was a high rate of over 96% complete resection and a very low conversion rate of 2.9%. Complications during surgery were not increased in the experimental group, and there was no difference regarding the pathological analysis.

Major post-operative complications at day 30 were 35.9% in the HMIO group and 64.4% in the open group. The combination of the ERAS programme with immunonutrition and a minimally invasive approach led to a significantly reduced risk of major post-operative complications at day 30 in the HMIO group of 69% (p<0.0001). This decrease is significantly linked to a decreased risk of major pulmonary complications: 18% compared to 30%. There was no significant effect on disease-free or overall survival although there was a trend towards lower mortality in the HMIO group.

To conclude, we have conducted a randomised trial which demonstrates that a minimally invasive approach to oesophageal cancer can reduce the rate of major complications, particularly major pulmonary complications, without having a negative impact on oncological outcomes such as recurrence or survival. This could set a new standard of care in oesophageal cancer surgery, combining a minimally invasive approach, peri-operative nutritional support, immunonutrition and ERAS programme, all these items leading to a significant decrease of post-operative complications.

References:


