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A position paper by the ESSO task force in collaboration with the ERAS society (ERAS coalition)**

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**PERIOPERATIVE NUTRITION AND ENHANCED RECOVERY AFTER SURGERY IN GASTRO-INTESTINAL CANCER PATIENTS. A POSITION PAPER BY THE ESSO TASK FORCE IN COLLABORATION WITH THE ERAS SOCIETY (ESSO-ERAS COALITION)**

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## **ABSTRACT**

Malnutrition in cancer patients, the prevalence and degree of which primarily depend on tumor stage and site. Preoperative malnutrition in surgical patients is a frequent problem, associated with prolonged hospital stay, more postoperative complications, higher re-admission rates and a higher incidence of postoperative death. Given the focus on the cancer and its cure, nutrition is often neglected or underevaluated, despite the availability of international guidelines for nutritional care in cancer patients and the evidence that nutritional deterioration negatively affects survival. Inadequate nutritional support for cancer patients should be considered ethically unacceptable; prompt nutritional support must be guaranteed to all cancer patients, as it can bring many clinical and economic advantages. Patients undergoing multimodal oncological care are at particular risk of progressive nutritional decline; it is essential to minimize the nutritional/metabolic impact of oncologic treatments and manage each surgical episode within the context of an enhanced recovery pathway. In Europe ERAS and routine nutritional assessment are partially implemented because of insufficient awareness of nutritional problems among health professionals, a lack of structured collaboration between surgeons and clinical nutrition specialists, old dogmas and the absence of dedicated resources. The collaboration between opinion leaders dedicated to Enhanced Recovery After Surgery from both the ESSO and the ERAS Society was born with the aim of promote nutritional assessment and perioperative nutrition with and without enhanced recovery program. The goal will be to improve awareness in the surgical oncology community and at institutional level to modify current clinical practice and identify optimal treatment options.

## INTRODUCTION

Malnutrition is a major clinical problem in patients with gastrointestinal malignancy; in surgical patients is associated with prolonged hospital stay, more postoperative complications, delayed recovery of bowel function, higher re-admission rates and a higher incidence of postoperative death [1]. Perioperative nutritional support has been introduced in many consensus and guidelines [2-4] including those from the enhanced recovery after surgery (ERAS) society for elective colon and rectal surgery [5,6]. Considering the negative impact of malnutrition on surgical outcomes in the setting of conventional perioperative care, there is evidence that preoperative nutritional status is a critical determinant of optimal outcomes for gastrointestinal cancer surgery [7].

Enhanced recovery after surgery (ERAS) protocols are multimodal perioperative care pathways designed to achieve early recovery after surgical procedures by maintaining pre-operative organ function and reducing the profound stress response following surgery. The key elements of ERAS protocols include preoperative counselling, optimization of nutrition, standardized analgesic and anesthetic regimens and early mobilization [6]. Despite the significant body of evidence indicating that ERAS protocols lead to improved outcomes, they challenge traditional surgical doctrine, and as a result their implementation has been slow.

Nutritional aspect is an essential component of enhanced recovery programs, including omission of pre-surgical fasting, oral carbohydrate load and early initiation of oral intake after surgery. However, there are no standardized protocols of diet progression before and after oncologic surgery. The studies examining the impact of nutritional status on the outcomes of gastrointestinal cancer surgery within an ERAS setting are very heterogeneous, so definitive conclusions can't be drawn [8].

The present position paper results from the collaboration between opinion leaders dedicated to Enhanced Recovery After Surgery from both ESSO and ERAS Society. The aim of the paper is to emphasize the importance of preoperative nutritional status on the short-term outcomes of an ERAS program for gastrointestinal cancer surgery, in order to favor the incorporation of nutritional issues and ERAS philosophy in daily practice. Among the different aspects of perioperative management, the key issues for a best practice approach to gastrointestinal surgical oncology patients must be nutrition assessment, frailties management, prehabilitation and minimally invasive surgery.

## **IMPORTANCE OF STANDARD ERAS**

Enhanced recovery is a multimodal perioperative care pathway designed to achieve early recovery by attenuating the surgical stress with a significant reduction in postoperative complication by 30 to 40% [9]. This is based on more than twenty evidence-based interventions covering all areas of the patients' journey throughout the surgical process [10]. Various terminologies (Fast-track, Enhanced Recovery Programm) with different protocols are described in the literature. The ERAS (Enhanced Recovery After Surgery) Society [11] was the first to publish international consensus guidelines for colorectal surgery [12] and then extended to various other surgeries. The use of standard ERAS as described by the guidelines is essential in order to have a common language worldwide. This allows internal and external reproducibility, as well as comparison between different centers. Consequently, multicentric studies can be conducted and published [13]. Moreover, a standardized ERAS implementation is also a key element for sustained beneficial results over time [14]. Therefore, a well-established and standardized ERAS is essential for evidence-based management of patients.

## **THE NEED FOR NUTRITIONAL SCREENING AND SUPPLEMENTATION IN MALNOURISHED PATIENTS**

The influence of nutritional status on postoperative morbidity and mortality has been well documented in both retrospective and prospective studies. Inadequate oral intake for more than 14 days is associated with higher mortality. The energy and protein requirements can be estimated with 25-30 kcal/kg and 1.5 g/kg ideal body weight.

Two multivariate analyses have shown, for patients undergoing surgery for cancer, that undernutrition is an independent risk factor for increased complications and mortality, length of hospital stay, and costs [15,16].

The prevalence of malnutrition is range from 15% to 60% in hospitalized patients and increase up to 71% in cancer [17]. Malnutrition is also related to cachexia and sarcopenia; the pathophysiology of weight loss in these patients may be related to a combination of undernutrition, inflammation and cancer induced catabolism [18]. A recent meta-analysis has clearly shown that sarcopenia is an independent prognostic factor for complications and survival following oncological surgery [19].

Identification of malnutrition is especially important for patients with cancer who undergo surgery, being associated with significant catabolic changes including net fat oxidation and lean tissue loss.

Implementation of neoadjuvant chemotherapy as standard of care for cancer patients represents an additional nutritional concern; in a study of patients with esophageal cancer the rate of malnutrition increased to 22% after neoadjuvant chemotherapy ( $p = 0.046$ ). [20] Improvement in nutritional status can decrease the infection rate in critically ill patients. In a RCT assessing the effects of parenteral nutrition support in orally undernourished patients, a decrease in nosocomial infections was observed among supported vs not supported patients ( $p = 0.02$ ). [21]

It is essential to minimize the nutritional/metabolic impact of both surgery and multimodal treatments by identifying patients in need for nutritional interventions. PG-SGA has been accepted as malnutrition assessment tool for the oncology population and has been used in many studies [22]; sarcopenia can be easily quantified using preoperative CT scans and its detection can be used to improve the clinical management of sarcopenic cancer patients [19]

Perioperative care must include nutrition into the overall patient management by avoiding long periods of preoperative fasting, re-establishing early postoperative oral feeding and starting nutritional therapy as soon as a nutritional risk becomes apparent. The ERAS protocol follows these principles strictly (preoperative carbohydrate loading, early PO feeding), allowing a significant reduction of length of hospital stay both in patients undergoing minor and major abdominal surgery [23,24].

The role of oral nutritional supplements (ONS) in malnourished patients is well established; in a recent RCT patients with colorectal cancer with pre-operative weight loss  $>1$  kg/3–6 months were randomized in receiving 250 mL/day ONS (10.1 KJ and 0.096 g protein per mL) and dietary advice vs dietary advice alone. Compared with dietary advice alone, ONS patients had fewer infections and less weight loss after surgery for colorectal cancer [25].

The role of nutritional supplements in well-nourished surgical patients remain debated. In a polish RCT [26] patients without malnutrition received ONS for 14 days before surgery or were kept on their everyday diet (control arm). In postoperative period, patients in control group had significantly higher ( $p<0.001$ ) serious complications compared to patients receiving nutritional supplementation. Moreover, levels of all laboratory parameters declined significantly ( $p<0.001$ ) in these patients, while stable or increased in interventional arm (albumin and total protein) or (transferrin and total lymphocyte count) respectively.

A recently published Cochrane review [27] failed to observe any significant benefit of early postoperative enteral feeding in colorectal patients, but the 14 studies analyzed were either small or of poor methodology.

Patients at moderate or severe nutritional risk (especially those undergoing upper GI cancer surgery) should be considered for routine post-operative nutritional support (where relevant by oral or enteral route) and consideration should be given to extending such support when the patient is discharged into the community [28,29]

## **PREHABILITATION**

In cancer patients, the impairment of aerobic capacity negatively affects preoperative functional reserve and increases the risk of postoperative complications [30]. Often, these patients have a low muscle mass due to undernutrition and /or cancer-related muscle catabolism. Recent studies suggest that several cytokines produced by the tumor or secreted by the host in response to the tumor induce muscle hypercatabolism [31].

Cancer-associated systemic inflammation causes a greater need for glucose as substrate to support inflammatory tissue and immune cells. Therefore, part of the muscle mass is converted to glucose via gluconeogenesis. As consequence, a rapid loss of muscle mass and a decrease in muscle function occur. In cancer patients, sarcopenia has been associated with a worse physical performance, reduced response to chemo-radiotherapy, increased postoperative morbidity and mortality, and a reduced life expectancy [32-36]. Sometimes, low muscular protein availability is associated with an increased visceral adipose tissue resulting in sarcopenic obesity. An excess of visceral fat is a source of pro-inflammatory cytokines and leptin, which influence insulin resistance and energetic metabolism. The combination of visceral obesity and sarcopenia reduced the chance to rescue patients from major postoperative complications and increased the likelihood of postoperative mortality [37-39].

There are some evidences that optimizing body composition and enhancing oxygen uptake ability before surgery may contribute to improve postoperative outcome. A multimodal prehabilitation program including physical exercise, nutritional supplements, and anxiety reduction strategies can optimize patient's body composition and physical performance. In a randomized trial, a prehabilitation program enhanced patient functional recovery, reduced postoperative morbidity, and shortened hospital stay following colorectal surgery [40]. Similarly, a personalized prehabilitation program enhanced aerobic capacity and reduced postoperative complications in a randomized blind controlled trial carried out

in high-risk patients undergoing major GI surgery, [41]. Since prehabilitation programs were different for duration of the intervention (3-6 weeks) and type of exercise training, future studies should contribute to standardize the preoperative pathway.

## **THE MANAGEMENT OF FRAIL AND ELDERLY PATIENTS**

More and more elderly patients are surgically treated for cancer; frequently, these patients are frail and need special assessment and care. Within an older population, comorbidities and age-related cachexia and sarcopenia are more prevalent. This may have a negative effect on the patient's fitness and postoperative outcome. Cancer cachexia is associated with a mortality rate of up to 80% [18,42]. Weight loss is the most universal symptom of cancer cachexia. However, weight loss does not specify what is lost; this can be either skeletal muscle, adipose tissue, or both. So, assessing body composition may require detailed assessment by e.g. CT scan or MRI [43]. Of note, edema and tumor load may cause an increase in weight, potentially masking weight loss. Malabsorption and maldigestion are major drivers of weight loss in patients with pancreatic cancer and therefore also require assessment. Preoperative screening to identify vulnerable patients is essential since every frail and elderly (cachectic) patient presents with specific problems and comorbidities. For these reasons, patients who are at risk of complications should receive additional pre- and postoperative support. Moreover, timely interventions in case of complications is of importance, potentially reducing sequential complications and complication-related mortality (i.e. reducing "failure to rescue") [44]. Preoperative interventions (e.g. exercise, nutritional support, and pharmacological support) should be developed for vulnerable patients to improve outcome: the "better in, better out" principle. Nutritional evaluation and its prognostic implications is involved in the very important aspect of assessing treatment goals together with patients. Integral part of the risk assessment, this could be decision determinant for alternative less invasive treatment or even no treatment at all.

## **THE ROLE OF IMMUNONUTRIENTS**

In recent years, standard nutritional formulas have been modified by the addition of arginine, omega-3 fatty acids, glutamine, and other components, which may increase immune responses by modulating inflammatory responses or enhancing protein synthesis after surgery. The potential effects of immunonutrients include reducing infectious and other postoperative complications. Significant benefits regarding infectious complications

were found for the pre-, peri- and postoperative use of the immunomodulating diet. [45]. The non-infectious complications and the hospital length of stay were reduced in case of peri- or post- operative initiation of the diet. The meta-analysis from Osland et al. and Song et al. [45,46] confirmed the benefits for the perioperative and sole postoperative use; the superiority of immune-enriched supplements has not been proven in the preoperative period, as no significant differences were found either in the complication rate or in functional capability and body weight.

The SONVI Study [47] has shown that the combination of ERAS care and immunonutrient supplements can reduce postoperative complications. Patients receiving immunonutrients preoperatively and postoperatively had fewer complications (primarily infectious) than those who received standard supplements.

Several meta-analyses of randomized controlled studies have shown that patients undergoing major surgery (including for cancer) may have reduced infectious complication rates and lengths of stay in hospital when given an immune enhancing feed rather than a standard isocaloric, isonitrogenous feed [46,48-51]. However, a strong evidence is still lacking. A recent study [52] evaluated the potential benefits of different combinations of immunonutrients in major abdominal surgery on mortality, morbidity and length of hospital stay (LOS). A total of 83 RCTs with 7116 patients were evaluated. Taking all trials into account, immunonutrients reduced overall complications, infectious complications and shortened hospital stay compared with control groups with a grade of evidence from low to moderate. These effects vanished after excluding trials at high and unclear risk of bias: non-industry-funded trials reported no positive effects for overall complications whereas those funded by industry reported large effects. This bias clearly lowers confidence in the existing evidence.

## **SURGICAL TECHNIQUE - INSTRUMENTATION**

In abdominal surgery, laparoscopic techniques decrease the trauma to the abdominal wall and peritoneum, and additionally particularly meticulous technique in the operative field is mandatory. This generally results in less blood loss, decreased surgical stress response, less postoperative pain and discomfort, earlier return of bowel function and quicker recovery. Together with the decreased incidence of wound complications this leads to decreased hospital stay compared to open surgery. The development of laparoscopic techniques had the same goals and ran parallel to the development of the first ERAS protocols, even if those were initially designed for open surgery. It has become clear that

incorporation of laparoscopic techniques in ERAS protocols further enhance outcome. This was demonstrated in the four-arm randomized LAFA trial where combined laparoscopy/fast-track arm had a shorter hospital stay than the open and non-fast-track arms. [53]. The current evidences suggest that laparoscopic techniques and ERAS protocols work highly synergistic. The decrease in surgical trauma after minimal invasive surgery is one important element to improve recovery after surgery. Thoracic epidural anesthesia was highly important for pain control in open surgery, but less so with laparoscopic surgery, and many centers have adapted their protocols accordingly [54]. Laparoscopic instrumentation has gradually improved and high definition optical systems improved vision to overcome inherent difficulties of laparoscopic surgery. There is however still room for technical improvement that will allow a wider use of minimal invasive techniques in more surgical areas. The cost issue should also be addressed by the manufacturing companies, in order to allow a more global implementation.

In addition to laparoscopic instrumentation there are also other areas of technical progress that can benefit patients. Surgical navigation and incorporation of perioperative imaging methods can allow for more precise localization of tumors or metastases and for more targeted resection or intervention, also decreasing surgical trauma. Anastomotic healing is an important determinant in the outcome of gastrointestinal surgery, and further improvements in stapler design and perfusion assessment could help to decrease anastomotic leaks. A more controversial area of technical progress is robotic surgery, with more degrees of freedom, 3D view, more stability etc. The exact benefit remains to be established, and the economic aspects will be highly important in determining implementation. In a randomized controlled trial of robotic-assisted vs laparoscopic rectal cancer surgery, [55] there were neither significant differences in conversion rates to open surgery nor in complication rates and quality-of-life outcomes. The health care costs in robotic-assisted laparoscopic group were significantly higher than in the laparoscopic group.

In addition to the short-term benefits, the assessment of new technology also concerns the long term oncological safety. For colon cancer, a Cochrane analysis has convincingly shown that oncological outcome is not different between open and laparoscopic approach [56]. For rectal cancer, oncological equivalence was not demonstrated clearly and further studies are needed. [57,58]. For esophago-gastric, pancreatic cancer and liver metastases [59-62] comparative cohort series suggest that, with proper selection, the oncological outcome may not be compromised.

## **IMPACT ON HEALTH CARE COSTS**

Steady increases in health care costs expressed as a portion of Gross Domestic Product are observed worldwide. Therefore, cost reductions are a main issue in most healthcare systems. It is now well established that successful implementation of ERAS leads not only to an improvement in postoperative outcome but also to a significant reduction of costs, estimated between 1800 to 8000 Euros per patient [63,64]. The sustained implementation of ERAS programs requires additional resources, both clinical (ERAS dedicated nurse, training and dedicated time for the ERAS team and nutrition assessment) and technical (ERAS Interactive Audit System, goal-directed fluid therapy monitoring, carbohydrate drinks, nutritional integration). Taking into account these costs, ERAS is still associated with a positive return on investment (ROI) [65,66]. Direct savings are obtained in decreased resource utilization with reduced laboratory tests and radiological procedures, and mostly in decreased length of stay [63]. By multiplying length of stay reductions (at least 1 to 2 days) [67,68] by annual patient load, the annual impact on inpatient bed-days saved can be estimated for each institution. In conclusion, implementation of ERAS programs is a powerful tool to decrease costs, essential issue in modern healthcare.

## **CONCLUSIONS**

Malnutrition is particularly common in gastrointestinal surgical oncology and may affect over 50% of patients. Nutrition is an important component of ERAS, and nutrition status is an independent predictor of clinical outcome. In patient groups within ERAS program, nutrition recommendations should be properly integrated to achieve optimal perioperative care and to reduce operative risk, especially in malnourished patients.

Preoperative optimization of patients is an essential part in successful outcome. Screening for malnutrition and sarcopenia is one of the important elements within a multimodal ERAS program because malnourished patients have worse surgical outcomes, like increased postoperative morbidities, delayed recovery of gastrointestinal function, and prolonged hospitalization.

The ultimate benefits of mini invasive surgery and ERAS are improved outcomes and faster recovery; given that laparoscopic surgery has been shown to improve outcomes alone or as a part of ERAS. Today, laparoscopy is considered as integral component to any ERAS protocol where applicable.

In Europe ERAS and routine nutritional assessment are part of the common practice in a minority of cases only, or are partially implemented with limited advantages for the patients. This could be related to insufficient awareness of nutritional problems among health professionals, lack of structured collaboration between surgeons and clinical nutrition specialists, old dogmas and the absence of dedicated resources. In view of the above considerations, nutritional support and ERAS pathways may still represent a neglected right for cancer patients. This issue is particularly disturbing as robust supporting scientific evidence is available.

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