Editorial Commentary

Immunonutrition in the esophagectomy patient: food for thought

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Nutritional status is an important factor that can influence the postoperative course in patients undergoing major cancer surgery. For patients with esophageal cancer, concern for malnutrition is especially important as more than 50% of patients present with weight loss at the time of diagnosis (1,2). Optimizing perioperative nutrition has been an important part of many esophagectomy care pathways and protocols. The American Society for Parenteral and Enteral Nutrition (ASPEN) formally recommends that patients undergoing major gastrointestinal surgery who are malnourished or at-risk of becoming malnourished receive perioperative enteral nutrition (3). However, our traditional understanding of the role of nutrition for improving postoperative healing and reducing complications is evolving, especially as more studies are published on the immune-modulating properties of nutrition and its impact on regulating the inflammatory response after major cancer surgery.

Significant postoperative stress has been associated with the onset of the systemic inflammatory response syndrome (SIRS). The activation of SIRS has been postulated to lead to a compensatory anti-inflammatory response syndrome (CARS) (4,5). Imbalance between these two pathways has been suggested to lead to a release in cytokines, which in turn can lead to downstream harmful effects including end-organ damage and infection (4,6). Enteral nutrition specifically designed to modulate the immune response, or immunonutrition, has been receiving increased attention for its purported benefits in reducing postoperative systemic stress. Immunonutrition often includes essential elements like arginine, glutamine, omega-3 polyunsaturated fatty acids (ω-3 PUFAs) and antioxidants (2,7). These immune-enhancing substrates have been shown to boost host immune responses, in turn controlling inflammatory responses that can occur after surgery and lead to organ dysfunction and/or increase risk of infection. In surgical patients with gastric and colorectal cancer, immunonutrition has been associated with decreased postoperative infection risk and reduced length-of-stay (LOS) (8-10). However, few studies have studied the impact of immunonutrition exclusively in patients undergoing esophagectomy (10,11).

Abe and colleagues performed a single-center retrospective cohort study to investigate postoperative stress in patients who received perioperative immunonutrition supplementation enriched with glutamine, fiber, and oligosaccharides (GFO®; Otsuka Pharmaceutical Factory, Inc.; Tokushima, Japan) (6). They hypothesized that addition of these specific elements to traditional enteral nutrition can aid in enhancing intraepithelial intestinal lining integrity and maintaining healthy gut flora, thus potentially preventing possible gut bacterial translocation that may occur in the setting of postoperative stress. This would in turn ostensibly lead to decreased likelihood of developing infectious complications and activation of SIRS. The authors utilized propensity score matching to study 89 patients who elected to receive perioperative GFO supplementation and 89 patients who received their institution's standard perioperative immunonutrition (IMPACT, AJINOMOTO Pharma; Tokyo, Japan). They measured markers of inflammation including C-reactive protein (CRP) levels and lymphocyte/neutrophil ratios before and after surgery. Additionally, the authors measured clinical outcomes including onset and duration of SIRS, postoperative complications, LOS, and overall

survival. The authors found that duration of SIRS was significantly lower in the group receiving GFO (0.74 *vs.* 1.52 days). Additionally, CRP was significantly lower in the GFO cohort by postoperative day 2, and the L/N ratio recovered faster in the GFO cohort by POD 3. Both cohorts were similar in the remainder of the outcomes, including incidence of postoperative infection and LOS. Abe *et al.* concluded that supplementation with glutamine, fiber, and oligosaccharide was beneficial to reduce early postoperative stress; they recommended the addition of such immunonutrition to esophagectomy perioperative care protocols.

The findings brought forth by Abe and colleagues are an important contribution to the limited studies available that have exclusively studied immunonutrition in esophageal cancer patients. However, conclusions stemming from the existing pool of evidence are overall mixed. There have been a handful of randomized controlled trials (RCTs) that have compared perioperative immunonutrition to standard enteral diets in esophagectomy patients (2,10). Kanekiyo and colleagues conducted a randomized study of 40 esophagectomy patients randomized to either receive standard enteral nutrition (Ensure, Abbott Laboratories, Ireland) or IMPACT (Nestle Health Science, Vevey, Switzerland). IMPACT is an immunonutrition supplement which contains arginine, ω-3 PUFAs, and RNA (11). Patients received either formulation for 7 days before and 7 days after surgery, after which they were transitioned to oral intake only. They measured multiple outcomes including incidence of postoperative infections, nutritional status markers (retinol-binding protein, prealbumin, transferrin), inflammatory markers (lymphocyte count, CRP), intensive care unit (ICU) LOS, hospitalization LOS, major morbidity, and long-term OS. The authors found a significantly lower incidence of infectious complications (pneumonia and surgical site infection) and lower duration of antibiotic use in the cohort receiving IMPACT. However, the remainder of the outcomes was similar between cohorts. Ryan and colleagues performed a double-blinded RCT to evaluate outcomes associated with administering nutrition supplemented with eicosapentaenoic acid (EPA), a type of ω-3 PUFA (12). EPA has been postulated to help modulate tumor-related pro-inflammatory cytokine production that is related to catabolism and cancer-related cachexia. In their study of 53 patients, 28 received an EPA-enriched formula (ProSure, Abbott Laboratories, Ireland) while the remainder received standard enteral nutrition (Ensure Plus, Abbott Laboratories, Ireland) for 5 days pre and 21 days post-surgery. They measured changes in lean body mass, duration of SIRS, and postoperative complications. Additionally, they measured an exhaustive panel of acute phase response, cytokine, and coagulation markers including albumin, CRP, pro-thrombin time, platelets, D-Dimer levels, TNF-alpha, γ-interferon, IL-2, IL-4, Il-1, IL-8, and IL-10. The authors found that patients who received EPA-enriched nutrition had improved maintenance of lean body mass after surgery and a significantly attenuated stress response (measured by trends in TNF-alpha, IL-10, and IL-8) compared to the control group. Interestingly, a study by Healy *et al.* (of the same study group) repeated this study using a multicenter randomized sample of 193 patients and examined similar outcomes over a 6-month period (13). They observed no differences by treatment protocol. These studies highlight the heterogeneity in study results, preventing a clear-cut conclusion to be drawn on the additional benefit gained by supplementing diets with specific immunonutrition formulas.

Several limitations exist in the ability to effectively evaluate the impact of immunonutrition for esophagectomy patients. The majority of available studies (both retrospective and prospective) have limited sample sizes and are underpowered. Abe and colleagues were only able to retrospectively evaluate 198 patients, which leaves the study underpowered to know whether administration of GFO was truly associated with decreased SIRS duration (6). The ability to recruit sufficient sample sizes may be multifactorial. Immunonutrition, compared to standard enteral nutrition, is still relatively new with most studies of esophagectomy patients only being published within the past 10 years (2,10). Thus, immunonutrition may not be widely implemented in perioperative nutrition protocols. Additionally, compliance with nutrition regimens can be challenging as patients are reluctant to use their enteral nutrition and tube feeding complications can be commonly observed (14). In a review of feeding-routes after esophagectomy, Berkelmans and colleagues noted that minor complication rates associated with feeding tubes has been reported to be anywhere from 13% to 38% (15). However, challenges to understanding the role of immunonutrition extend beyond sample size and power.

It is unclear which component of immunonutrition has the most immune-boosting effect as these components have not been studied individually in a clinical population of esophagectomy patients. Additionally, the proposed mechanisms of how each component contributes to immune system modulation are diverse and not fully understood. For example, glutamine is a major component of the formula

studied by Abe and colleagues. Glutamine has been shown to be depleted in patients undergoing trauma or severe postoperative stress, and has several proposed roles (16). Glutamine can easily convert to glutamic acid, which is an essential component for the production of glutathione, an antioxidant. Glutathione levels have been shown to be depressed in patients with human immunodeficiency virus (HIV), Hepatitis C, and cirrhosis (16). It has been proposed to have a role in inhibiting the inflammatory response by counteracting oxidant molecules that can activate regulators associated with release of cytokines, including NF-κB (16). In addition to serving as a substrate for glutathione production, glutamine has been proposed to aid in maintaining gastrointestinal epithelial lining. Multiple animal studies have shown that glutamine supplementation may play a role in increasing intestinal epithelial proliferation, reducing apoptosis, and regulating functions of tight junction proteins that are essential for inhibiting bacterial translocation (17). Additional studies have suggested that glutamine may increase the expression of heat shock proteins, which are upregulated in times of major stress (18). Heat shock proteins are important in inducing a state of "stress tolerance" to ensure that the host stress response does not lead to overwhelming inflammation that could potential be fatal. Given that the physiologic mechanisms for immunonutrients are complex and diverse, studying the downstream effects of immunonutrients is problematic.

Appropriate and focused endpoint selection for immunonutrition studies is a challenge. Given the diverse array of markers suggested to be influenced by immunonutrients, many studies have included a myriad of laboratory endpoints including lymphocyte and neutrophil count, various cytokines, TNF-alpha, and markers of acute phase reactants (11-13). At times, it is hard to make clinical sense of the results due to the overwhelming abundance of laboratory tests being evaluated. Additionally, these studies are often underpowered to detect true changes in these laboratory tests. Furthermore, it is difficult to pinpoint which marker is the most important to measure, or what truly defines meaningful changes in the levels of these markers. Even when changes are detected in these laboratory markers, whether this translates to clinical significance is debatable. The likelihood of institutions investing in immunonutrition protocols will be based off whether there are benefits observed in meaningful short and/or long-term clinical outcomes. However, the literature overall is mixed as to whether esophagectomy patients who receive immunonutrition experience true clinical benefit. Abe and colleagues suggested that patients who received GFO supplementation may experience on average <1-day shorter duration of SIRS, with faster return of lymphocyte/neutrophil ratio and CRP level back to normal (6). However, these patients failed to exhibit benefit in more traditional clinical outcomes, including infectious complications and LOS. Thus, while it is possible that supplementation with glutamine, fiber, and oligosaccharides likely confers some benefit to esophagectomy patients, it is difficult to conclusively say based on Abe and colleagues' study. Findings from the existing literature do not help, as the pool of studies focused on esophagectomy patients do not consistently find significant changes in clinical outcomes associated with addition of immunonutrition formulas.

Finally, heterogeneity in patient populations and protocols introduce a barrier to interpretation and generalizability of results. Esophageal cancer patients present in a variety of states of malnutrition. Given differences in baseline presentation, patients may require more personalized recommendations for supplementation to achieve adequate nutrition goals. Retrospective methods including multivariable analysis and propensity matching are unable to account for all patient-level differences. Additionally, there are differences among studies in the types of immunonutrition formulas being tested, the types of control enteral nutrition being given, and the quantity and duration these protocols require. For example, Abe *et al.* used GFO and IMPACT (another immunonutrition formula) as their intervention and control formulas, respectively. However, there are a multitude of immunonutrition formulas currently available, and each of these formulas has a different nutritional makeup. Different formulas have been studied in different durations and quantities, extending from 5–7 days preoperatively and 5–21 days postoperatively (6,13). Finally, heterogeneity in perioperative care and surgical practices can potentially impact the ability to generalize results. For example, Abe and colleagues routinely administered methylprednisolone to all patients thirty minutes before surgery, which may impact the ability of patients to mount a SIRS response at baseline (6). Perioperative methylprednisolone is not routinely given in many institutions, further limiting generalizability of the findings to esophagectomy patient populations at large.

While there are inherent challenges to assessing the role of immunonutrition in patients undergoing esophagectomy, it does not mean that future efforts to understand the potential benefits should be thwarted. A multicenter collaboration could assist in this effort and provide a

variety of benefits. First, there could be a greater chance to accrue sufficient sample sizes to provide a well-powered study. Additionally, a multicenter study could allow for the standardization of the formulas being assessed and the protocol used for administration. This would limit the significant heterogeneity that currently exists in the literature, the majority of which are single-institution studies or trials. Furthermore, a consensus could be reached to ensure that clinically meaningful endpoints are selected and measured in a well-powered manner. Finally, with a large enough sample size, subgroup analyses could be performed to assess how variations in patient characteristics affect outcomes to identify which patients benefit the most from immunonutrition. Obtaining higher quality evidence that demonstrates a clear and clinically meaningful benefit for the adoption of immunonutrition protocols is necessary prior to a widespread change in the management of nutrition in patients undergoing esophagectomy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Daly JM, Fry WA, Little AG, et al. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. J Am Coll Surg 2000;190:562-72; discussion 572-3.
2. Mimatsu K, Fukino N, Ogasawara Y, et al. Effects of Enteral Immunonutrition in Esophageal Cancer. Gastrointest Tumors 2018;4:61-71.
3. Directors ASfPaENASPENBo. Clinical Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients, 2009. JPEN J Parenter Enteral Nutr 2009;33:255-9.
4. Dąbrowska AM, Słotwiński R. The immune response to surgery and infection. Cent Eur J Immunol 2014;39:532-7.
5. Suchner U, Kuhn KS, Fürst P. The scientific basis of immunonutrition. Proc Nutr Soc 2000;59:553-63.
6. Abe T, Hosoi T, Kawai R, et al. Perioperative enteral supplementation with glutamine, fiber, and oligosaccharide reduces early postoperative surgical stress following esophagectomy for esophageal cancer. Esophagus 2019;16:63-70.
7. Grimble RF. Immunonutrition. Curr Opin Gastroenterol 2005;21:216-22.
8. Cheng Y, Zhang J, Zhang L, et al. Enteral immunonutrition versus enteral nutrition for gastric cancer patients undergoing a total gastrectomy: a systematic review and meta-analysis. BMC Gastroenterol 2018;18:11.
9. Xu J, Sun X, Xin Q, et al. Effect of immunonutrition on colorectal cancer patients undergoing surgery: a meta-analysis. Int J Colorectal Dis 2018;33:273-83.
10. Mudge L, Isenring E, Jamieson GG. Immunonutrition in patients undergoing esophageal cancer resection. Dis Esophagus 2011;24:160-5.
11. Kanekiyo S, Takeda S, Iida M, et al. Efficacy of perioperative immunonutrition in esophageal cancer patients undergoing esophagectomy. Nutrition 2019;59:96-102.
12. Ryan AM, Reynolds JV, Healy L, et al. Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. Ann Surg 2009;249:355-63.
13. Healy LA, Ryan A, Doyle SL, et al. Does Prolonged Enteral Feeding With Supplemental Omega-3 Fatty Acids Impact on Recovery Post-esophagectomy: Results of a Randomized Double-Blind Trial. Ann Surg 2017;266:720-8.
14. Huerter ME, Charles EJ, Downs EA, et al. Enteral Access is not Required for Esophageal Cancer Patients Undergoing Neoadjuvant Therapy. Ann Thorac Surg 2016;102:948-54.
15. Berkelmans GH, van Workum F, Weijs TJ, et al. The feeding route after esophagectomy: a review of literature. J Thorac Dis 2017;9:S785-91.
16. Kim H. Glutamine as an immunonutrient. Yonsei Med J 2011;52:892-7.
17. Kong S, Zhang YH, Zhang W. Regulation of Intestinal Epithelial Cells Properties and Functions by Amino Acids. Biomed Res Int 2018;2018:2819154.
18. Wischmeyer PE. Glutamine and heat shock protein expression. Nutrition 2002;18:225-8.

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