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Nutrition in the Neoadjuvant Gastric Cancer Patient, is early administration appropriate?

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Purpose: Gastric cancer is one of the world's leading cancers. Despite the availability of testing, patients often present with advanced (stage III or stage IV) gastric cancer. These patients are always in a state of malnutrition and sarcopenic secondary to pain, loss of appetite, nausea, vomiting and dysphagia. Treatment for this cancer includes radical surgery, sometimes chemotherapy and rarely radiotherapy. Nutrition is critical to patient outcomes during chemotherapy, surgery, and healing; many measures are already in place to improve nutrition in these patients. This literature review looks directly at the use of enteral feeding (EN) of gastric cancer patients in conjunction with neoadjuvant chemotherapy (NACT).
Methods: The research focuses on the keywords nutrition, gastric cancer, enteral feeding and neoadjuvant nutrition. Several search engines used included National Center for Biotechnology Information (NCBI), PubMed, QxMD Read, Science Direct, and a search conducted through Alberta Health Services Knowledge Resource Service (KRS).
Results: The combined information within each of the articles reviewed recognized that early nutrition supplementation had positive impacts on maintaining albumin levels, increased patient's immunity, improved healing and shortened length of hospital stay.
Conclusion
All patients receive nutrition throughout their hospital stay; research indicates that the earlier nutrition is given to a patient, the better the overall outcomes of chemotherapy, surgery, shortened length of stay, and quality of life.

Keywords
nutrition, gastric cancer, enteral feeding and neoadjuvant nutrition.

INTRODUCTION

Gastric cancers are still, despite education, improved lifestyles and better screening, one of the most common cancers worldwide.[1] Surgery offers the only curative treatment modality for lymphomas and maltomas.[2] With major surgical interventions, it is known that nutritionally depleted patients have poor healing outcomes; thus, is early support of dietary nutrition via parental or enteral gastric feeds essential for patient success? This paper reviews pertinent articles and studies to see whether patients receiving nutritional support from early neoadjuvant chemotherapy (NACT) have a better prognosis with a shorter stay in hospital. NACT is used in gastric cancer patients to help downsize or debulk the tumour.

METHOD

Early in gastric cancer conditions, before chemotherapy, parental and enteral feeding of patients is not a common practice. Literature searches conducted used the National Center for Biotechnology Information

(NCBI), PubMed, QxMD Read, Science Direct, and a search through Alberta Health Services Knowledge Resource Service (KRS). Due to the limited research on nutritional support before chemotherapy in gastric cancer patients, a review of thoracic journals was conducted; however, only to review the dietary effects on esophagectomy patients and their healing.

RESULTS

Results suggest that neoadjuvant chemotherapy (NACT) with enteral feeding (EN) provides needed nutrition to patients depleted of essential nutritional resources. EN provides better nutritional support than total parenteral nutrition TPN, increases albumin, immunity, reduces inflammation, decreases infection rate and increases healing. Furthermore, the articles propose a decrease in hospital length of stay.

DISCUSSION

Cancer Malnutrition

Malnutrition and cancer malnutrition are different. Tumour Necrotic Factor (TNF), originally known as cachectin, is a mediator in cancer's hypermetabolic and catabolic states. A patient with cancer malnutrition suffers from skeletal muscle loss and depressed energy because of inadequate nutritional intake and a metabolic imbalance. European Society for Clinical Nutrition and Metabolism (ESPEN) reviewed many articles in completing their guidelines for nutrition for cancer patients. ESPN notes elevated resting metabolic rates, insulin resistance, lipolysis, and proteolysis aggravated weight loss are provoked by systemic inflammation and catabolic factors, either host or tumour-derived.[3] The result is a metabolic imbalance. ESPEN further states that this kind of malnutrition can be partially reversed only with conventional methods.

Nutrition and Healing

A meta-analysis from the journal *Nutrition*[4] discussed basics in nutrition and healing with the focus on the three elements of recovery, inflammatory, proliferation and maturation and how each stage is affected by nutrition and the progression and regression without appropriate sustenance. The team noted how demanding the wound healing phase is on the body's energy stores. Healing needs to reproduce cells from depleted energy and protein stores and can be very challenging for undernourished patients. The journal discusses the need for increased protein to assist the healing of tissues and further remarks that the supplements are individualized for each patient. The wound healing processes are outlined in the *International Journal of Molecular Science's* article *Nutrition and Wound Healing*; *An Overview Focusing on the Beneficial Effects of Curcumin*." When the body has an injury, in this case, an incision, it creates a fibrin plug. This is necessary for bleeding control and as a barrier to infection. The fibrin plug also provides an extracellular matrix for cell migration and releases growth factors (e.g., platelet-derived growth factor—PDGF—and transforming growth factor—TGF), which draw cells to the wound. The inflammatory phase slows down leukocytes in the bloodstream; this allows them to move through endothelial gaps by binding to integrins in the extracellular area. WBCs, (neutrophils) and macrophages are recruited to the wound to

remove waste, creating a wide range of growth factors along with cytokines, which encourages fibroblast migration and proliferation. Immediately after tissue injury, cell hypoxia is a main trigger of keratinocyte migration, angiogenesis, fibroblast proliferation, and the freeing of growth factors and cytokines. Wound closure occurs when fibroblasts and endothelial cells produce the early granulation tissues beginning the processes of wound contraction. The extracellular matrix (collagen, enzymes, and glycoproteins) make available substrates for cell migration; this restores the function and integrity of the tissue. The construction

of new blood vessels re-establishes tissue perfusion, allowing for the return of oxygen supply and nutrients." [5] The need for the body to have a metabolism that supports the stages of healing requires nutritional support. Gastric cancer patients are often already working on depleted stores; further assault delays healing time, increasing opportunistic infections and reduced quality of life.

Patient-Generated Subjective Global Assessment

In assessing a patient's nutritional state, various scales have been developed. The Patient-Generated Subjective Global Assessment (PG-SGA) is the gold standard[6] for assessing nutrition and is a proactive test initiated on each patient. The PG-SGA reviews several metabolic questions, weight loss, BMI, skinfold measures and handgrip strengths, allowing specific nutritional parameters. This assessment can help predict postoperative complications, length of hospital stay, quality of life, and potentially survival. [7] The PG-SGA is a dynamic assessment, changing as the patient's nutritional state changes. The PG-SGA is a cycle initiated with an assessment/diagnostic reasoning and patient frailty, followed by diagnosis, where nutritional status is reviewed, observing for sarcopenia, cachexia and determining the patient's nutritional intake. The dietitian and the patient set goals and interventions initiated. This cycle is dynamic, and as the patient monitoring continues, new evaluations are determined. [8] To determine the patient's level of nutrition, laboratory studies specifically look at serum proteins levels of albumin, pre-albumin (PAB) and ferritin. Furthermore, micronutrients Vitamin A, B12, C, D, zinc, selenium, folate and chromium are reviewed for analysis.

Prognostic Nutritional Index

A search for preoperative EN identified numerous articles discussing the need for better-informed nutrition plans in the malnourished patient populations and the resulting poor post-surgical outcomes patients. The use of prognostic nutritional index (PNI) was discussed in many articles and indicated a low PNI was predictive means of poor long-term survival. The formula was calculated using the following: $10 \times$ serum albumin (g/dl) $+ 0.005 \times$ total lymphocyte count (per mm3).[9] As has been discussed in this paper already low albumin is associated with poor healing.

Parenteral/Enteral Nutrition

Total parenteral nutrition (TPN) and enteral nutrition (EN) are nutrition modalities that, as necessary, can circumvent the stomach yet are still able to provide appropriate nutrients. A feeding tube could be placed via a nasojejunal or nasoduodenal tube if a patient has a gastroesophageal junction tumour. There are numerous EN formulas already developed to meet the nutritional needs of each patient. Of the two modalities, EN has become the preferred method for providing artificial nutrition. From the *World Journal of Surgical Oncology*, the article "*Contemporary enteral and parenteral nutrition before surgery for gastrointestinal cancers: a literature review*" noted that since 1990, EN had been proven to reduce

postoperative mortality by 50–70% and perioperative complications by up to 50%. EN shortens the hospital stay, has fewer complications and reduces costs compared with TPN.[10] A study in the *Journal of Trauma Acute Care Surgery* indicated that between the two methods, EN was noted to have amino-acid repletion, urea cycle upregulation, restoration of antioxidants and increasing RNA synthesis, whereas TPN, although having increased amino-acid concentrations, it did not influence protein metabolism or antioxidant repletion.[11] In the *Journal of Investigative Medicine*, the article "*Enteral nutrition versus Parenteral nutrition after major abdominal surgery in patients with gastrointestinal cancer: a systematic review and meta-analysis*," reviewed 2540 patients and noted the 1268 patients receiving EN had a shorter hospital stay, shorter time to pass flatus and a significantly greater increase in albumin than the TPN group.[12] TPN does have a place in nutritional replacement. Anytime the gastrointestinal tract is not functional, TPN for patients with bowel obstruction, short periods for those with Ulcerative Colitis and Short Gut Syndrome is the means for nutrition supplementation. TPN is given through a peripherally inserted central catheter (PICC) line placed in the subclavian vein or through a central line. EN is often given either as a nasojejunal or nasoduodenal feeding tube or surgically placed into the small intestine as a jejunostomy tube. "*Complications of Feeding Jejunostomy Tubes in Patients with Gastroesophageal Cancer*," an article from the *Journal of Gastrointestinal Surgery*, conducted at one facility, reported most of the patients used the feeding tube after discharge. The intent of using this article is to provide relative information of possible complications when feeding jejunostomy tubes are used. According to the study, feeding jejunostomy tubes were inserted for total/completion gastrectomy (n=49/117, 41.9%), proximal gastrectomy (n=7/117, 6.0%), or esophagogastrectomy (n=61/117, 52.1%). Complications arose in 44% of the patients during their use. The team notes that the complications, for the most part, were not of serious nature (70.7%) and were easily correctable at home via a telephone call. Problems included dislodgement (n=22), clogging (n=13), and leakage (n=6). Three-point four percent required operative intervention for small bowel obstruction (n=3) and hemorrhage (n=1). Feeding jejunostomy tube complications were more common with gastrectomy than esophagogastrectomy (53.6% vs. 36.0%). The authors' presumption that this was due to the longer time feeding jejunostomy tubes are used in gastrectomy patients (71 vs. 38 days).[13] There are rare complications such as knot formations in feeding jejunostomy tubes; in fact, the authors of the literature review found only three such cases and feel the complication was due to the length of the tube.[13]

Preoperative Nutrition during Neoadjuvant Chemotherapy

The use of enteral feeding for patients receiving chemotherapy is not well documented in gastric cancer patients. The use of NACT is better documented in thoracic esophageal cancer patients, as the esophagectomy patients have limited means for receiving oral nutrition. The *World Journal of Gastrointestinal Oncology* in 2019 published a report titled "*Impact of regular enteral feeding via jejunostomy during neoadjuvant chemotherapy on body composition in patients with oesophageal cancer*." They examined the effect of enteral nutrition via a feeding tube and the overall body composition in patients undergoing NACT. This patient population was diagnosed with esophageal cancer and was undergoing esophagostomies with NACT. The patient's level of nutrition and the state of sarcopenia were established before treatment and followed up afterward. The use of measurements from CT at the level of the third lumbar vertebrae demonstrated whether or not the nutrition the patients were receiving maintained muscle mass, as the use of BMI can be misleading. The authors concluded, although there was no loss of body weight or changes in BMI from the continual nutrition supplement, the skeletal muscle waste was

significant at the lumbar measurement. The team further stated the need for multimodality interventions included nutrition and exercise, to improve patients' overall success.[13] Although this article, "*Randomized study of the clinical effects of ω-3 fatty acid–containing enteral nutrition support during neoadjuvant chemotherapy on chemotherapy-related toxicity in patients with esophageal cancer*," is specific to patients with esophageal cancer, the outcomes support this paper. Of note, omega-3 removes the arachidonic acid from the cell membrane, which does not allow for thromboxane to be produced, thus preventing clotting or the prostaglandins leading to inflammatory mediators. The researchers of this article questioned if omega 3 fatty acids in NACT EN were capable of reducing chemotherapy-related toxicity. This was a randomized

study with 61 participants receiving cisplatin. The patients were divided into two groups Omega 3 Rich and Omega 3 Poor. The primary outcome noted that the Omega 3 Rich formula cohort had a decreased amount of mucosal toxicities and increased hepatoprotection. Furthermore, the Omega Rich group had an increase in albumin comparison to the Poor group, which the team surmised may help to reduce chemotherapy-induced inflammation.[14]

The authors of the article, "*Effects of neoadjuvant chemotherapy combined with enteral nutrition in gastric cancer*" from Weifang People's Hospital, China, trialled two courses of 96 patients. The control group (48) was given NACT before surgery, whereas the observation group (48) was given EN before surgery. The EN supplement was orally. The team looked for changes in the immune indexes, inflammatory indexes and intestinal flora in each group. During their research, the authors noted that the observation group, that is, the group receiving EN, had decidedly better serum IL-2, IL-6 and IL-10 levels post-surgery, serum TNF-α and CRP levels after surgery. The post-surgery T-cell subsets, immunoglobulin, and intestinal flora were noted to have increasing Bifidobacterium and Lactobacillus, and reduction of Escherichia coli and Enterococcus compared to the control group. During their research, an article they referenced indicated that the combined use of NACT and EN had an even more profound effect. This study's conclusion indicated that NACT with EN reduces the degree of perioperative inflammatory responses, improves body immunity, and maintains intestinal flora structure.[15]

The "*Parenteral nutrition during neoadjuvant chemotherapy for patients with non-metastatic gastric or esophagogastric cancer to reduce postoperative morbidity (PERCOG) trial*" out of Germany is a 14 a randomized controlled multicenter observer-blinded trial, and an ongoing trial having completed recruiting in 2018 with a completion date 32 months post final treatment. This trial investigates if preoperative nutrition during NACT in the non-metastasized gastric cancer or cancer of the esophagogastric junction produces results proving a reduced rate of postoperative complications after surgery for malignancies of the upper gastrointestinal tract. PERCOG uses a parenteral formulation during its trial to support the enteral nutritional supplement in the experimental group, where the control group is not receiving a parenteral augmentation. We await the results of this trial.[15]

The authors of the article "*Nutrition in patients with gastric cancer: an update*." Note that preoperative nutrition directly affects postoperative outcomes, overall survival and disease-specific survival. As the team indicated, malnutrition is associated with poor post-surgical outcomes. Their study used the German S3 guidelines, which provide recommendations for patients with inadequate or insufficient dietary intake defined as oral intake less than 500kcal/day or less than or equal to 75% of required nutrition for greater than 1-2 weeks. This paper suggests that using EN with a nasogastric tube for a short period before surgery would be appropriate. However, if the EN was to be in place for a more extended period, considering an EN

tube via a jejunostomy more applicable. Although this article's focus was pre-surgery, it is not definitive as to prior or during NACT, and the study does note that it may take up to two weeks for appropriate nutritional status to be met.[16]

In patients with obstruction secondary to cancer mass, the following two articles discuss the use of enteral nutrition with NACT. The first paper, "*Nutritional support in progressive gastric cancer patients with obstruction during the neoadjuvant chemotherapy*." from the 2008 Chinese study, notes that of the 49 participants, only eight accepted the EN therapy. In contrast, the remaining patients continued on a regular diet with body weights, plasma protein, albumin, Hg and RBC levels recorded before and after

neoadjuvant chemotherapy. The group of eight receiving EN proved to have increased weight, significantly higher albumin and plasma protein with a slight increase of Hg and RBC in comparison to the 41 patients who remained on a regular diet and concluded that the use of EN in the presence of NACT could improve the patient's nutritional status.[17] The second paper, "*Efficacies of neoadjuvant chemotherapy plus nutritional support in advanced gastric cancer complicated with pylori obstruction*." Also, another article out of China reported that 116 patients were enrolled on the project into two groups. Group A consisted of two sub-groups EN and TPN and Group B, exploratory laparoscopic procedure only. The authors note the rate of excision/radical excision of group A (85.5%, 45.2%) was much higher than group B (64.8%, 18.5%) (both $P < 0.05$). Of the two groups, Group A's serum albumin and quality of life improved over Group B. The authors noted that in group A cadre, the EN patients had better ALB results than the TPN patients. Their conclusion indicated that patients receiving nutritional support, especially EN plus neoadjuvant chemotherapy, increased the rate of tumour excision.[18]

Finally, again, the use of the PNI score plays a vital role as it demonstrates a measurable linkage between poor nutrition and shortens survival outcomes. A Japanese article in the *Surgery Today Journal*, ("*A decrease in the prognostic nutritional index (PNI) is associated with a worse long-term outcome in gastric cancer patients undergoing neoadjuvant chemotherapy*,") studied 54 patients who had undergone R0 gastrectomy post NACT. The paper reviewed the patient's PNI. Their study was to calculate the PNI in patients receiving NACT. Their formula was computed using the following: $10 \times$ serum albumin (g/dl) $+ 0.005 \times$ total lymphocyte count (per mm3). Their observations noted that of the preoperative to postoperative patients undergoing NACT, who's PNI was decreased, had worse long-term outcomes in gastric cancer. [9] Although this study does not discuss nutrition and NACT directly, the knowledge brought from the research does show a correlation between low nutritional values during NACT and the poorer prognosis.

CONCLUSION

The nutrition of a patient with cancer is one of the basic factors which impacts on the safety of a surgery.[10]All the articles suggest that nutritional support plays a vital role in improving albumin, immunity, reducing infection and inflammation, assisting healing, and leading to shortened hospital stays. Predictive outcomes using PNI time and again prove the patients with lower nutritional status have shorter life expectations. Providing nutrition by means of EN during the NACT period rather than later does appear to show an increase in albumin, hepatic protection and a better overall survival rate. Although several studies correlated supported nutritional status before surgery results in increased healing and decreased hospital stays, there still needs to be further investigation to show that EN before or during NACT has better

outcomes than preoperative or waiting until post-op before providing that nutrition. The PERCOG study should offer increased data and possibly a move towards early nutrition.

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