IMMUNONUTRITION IN HEAD AND NECK CANCER SURGERY

by

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Abstract

Many nutrients are thought to impact the human immune response, whether as protagonists of healing, antagonists of inflammation, or both. Three of the most commonly studied "immunonutrients" include arginine, glutamine, and n-3 fatty acids. The purpose of this evidence analysis project was to determine if immunonutrition in the preoperative, perioperative or postoperative phases of head and neck cancer surgery could benefit outcomes such as length of stay and postoperative complications. This project was based on the Evidence Analysis Process defined by the Academy of Nutrition and Dietetics. This five-step process aims to critically evaluate current literature to form evidenced based conclusions. In total, seven studies were incorporated in this analysis. Four articles investigated immunonutrition in the form of arginine, one investigated glutamine and one investigated n-3 fatty acids. One article studied a combination of arginine and n-3 fatty acids together. There was also one systemic review with meta-analysis included. Overall, the articles included in this project generally found a correlation between immunonutrition in the perioperative or postoperative phase and improved post-surgical outcomes and length of stay. Immunonutrition in the perioperative phase potentially improves post-surgical outcomes and reduces length of stay in head and neck cancer patients undergoing surgical intervention.

Keywords: immunonutrition, head and neck cancer surgery, arginine, glutamine, n-3 fatty acids

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Chapter 1: Introduction to the Study

Head and neck cancers are a grouping of oncologic diagnoses that can have significant repercussions with nutrition status due to the location of the disease. It has been estimated that 3-52% of squamous cell carcinoma head and neck cancer patients are considered malnourished upon diagnosis (Gorenc, Kozjek & Strojan, 2015). The risk of malnutrition continues far beyond the initial diagnosis, as many patients experience intensive treatments such as chemotherapy, radiation therapy, or surgery that can further interrupt appetite and oral intake. Therefore, it is important for medical professionals, especially registered dietitians, to be proactive members of the care team and advocate for interventions that can improve the nutrition status of these high-risk patients. This chapter discusses the content of this Evidence Analysis Library (EAL) project, including the purpose, significance, and inner details of the research.

Background

Cancer is a highly metabolic disease state, and therefore nutrition status should be a central focus throughout treatment. On a more specific level, it is known and well-documented that head and neck cancer surgery can leave a patient nutritionally at risk, even malnourished. Generally, this high risk for malnutrition stems from the potential for mechanical difficulties and dysphagia following reconstruction. Although nutrition support may be used post-operatively, a patient can still fall short of nutritional needs if metabolic needs are higher than anticipated in the acute healing process.

The literature also emphasizes that "immunonutrients," such as glutamine, arginine, nucleotides, and omega 3 fatty acids, have the potential to help mitigate an immune response in the human body. In combining surgical pathways with immunonutrition, there may be a great potential to impact standards of care. To do so, detailed investigation of present literature was

needed to determine if these immunonutrients can improve outcomes in this high-risk population.

Problem Statement

With a population such as head and neck cancer surgical patients, consensus amongst medical professionals on best evidence-based practice becomes essential. Head and neck cancer patients that undergo surgical intervention are vulnerable to malnutrition and postoperative complications, yet there are no consensus guidelines on nutritional interventions to prevent these issues from occurring. Specifically, it is unclear whether immunonutrition reduces the risk of malnutrition in this population. Therefore, this evidence analysis project is crucial in assessing the present literature to develop evidence-based standards of care and improve outcomes of this population.

Purpose of the Study

In this evidence analysis project, the present literature on immunonutrition interventions (oral or enteral formulas) in the surgical head and neck cancer populations will be assessed. Through critical appraisal of articles, this project will be able to contribute to evidence-based guidelines by assessing the efficacy of immunonutrition in preventing postoperative complications in the setting of head and neck cancer patients.

Research Question

Does implementation of immunonutrition formulas in the pre-, peri- and/or post-operative phase reduce complications and improve outcomes for adult patients undergoing surgical intervention for head and neck cancer?

Significance

In a nutritionally at-risk population such as head and neck cancer, any intervention with the potential to positively impact outcomes needs to be carefully considered. Not only can a cancer diagnosis induce emotional and mental turmoil, but a patient at high nutritional risk can also face life-threatening complications. Therefore, this patient population is in need of well-reviewed, evidence-based practice guidelines that have the potential to improve survival outcomes.

This EAL project has the potential to improve postoperative surgical outcomes in a group that is historically at high nutritional risk. The findings of this project will lead to a consensus on the optimal timing of immunonutrition: preoperatively, postoperatively, or perioperatively; Therefore, it could significantly contribute to evidence-based care guidelines that will standardize care for the head and neck cancer population. Finally, this project could prove to be significant by increasing the use of immunonutrition interventions in not only head and neck cancer patients, but potentially extending to other cancers and diagnoses.

Nature of the Study

The nature of the Evidence Analysis Process involves a five-step procedure that leads to a consensus statement based on findings. The first step is to develop the Evidence Analysis question, otherwise known as the research question, using the PICO model. The Evidence Analysis question should reflect the population, intervention, comparison and outcomes of interest. Step two involves gathering and classifying the current evidence on the research question by implementing a thorough search plan and determining which articles to include and exclude. The third step entails critically appraising each of the included articles using the Evidence Abstract Worksheet (The Academy of Nutrition and Dietetics, n.d). and Quality

Criteria Checklist (The Academy of Nutrition and Dietetics, n.d). The final rating of each articles will be determined as positive (+), neutral (∅) or negative (-). Step four is when the evidence is summarized using the Evidence Overview Table provided by the EAL. Upon summarizing all information, step five entails writing the conclusion statement and grading it based on the Conclusion Grading Table from the EAL Manual (The Academy of Nutrition and Dietetics, n.d).

Assumption

In any research study or project, it is pertinent to address assumptions as well as any possible limitations or delimitations. In this project, it is assumed that all studies included in the EAL are methodologically fit and reliable.

Limitations

Every study's design should be assessed for limitations that may threaten the validity of the findings. These limitations can impact how generalizable the findings are to the population as well. A major limitation of this evidence analysis project is that many of the studies regarding immunonutrition in cancer surgery patients have small sample sizes, and those with larger samples are often not exclusive to head and neck cancer. Small sample sizes limit the generalizability of the study results to the head and neck cancer surgery population as a whole. Another limitation of this project is that immunonutrition formula composition varies between studies, making it difficult to generalize to all immunonutrition products.

Delimitations

Delimitations were put in place for this evidence analysis project in order to define a concise, focused search of the present literature.

The inclusion criteria include:

i. Literature only involving adult subjects with head and neck cancers, undergoing cancer surgery
ii. Time frame of included research defined as “research within the last 20 years (2000 or later) for randomized control trials or written in the last 20 years (2000 or later) for meta-analyses and reviews
iii. Meta-analyses and reviews can include research > 20 years old.

Exclusion criteria for this EAL project is defined as:

i. Pediatric subjects
ii. Research based on cancers outside of the head and neck regions
iii. Non-surgical patients
iv. Study size fewer than 15 participants in either study group (intervention or control)
v. Research prior to the last 20 years (published earlier than 2000) for randomized control trials or written prior to 20 years ago (prior to 2000) for meta-analyses and reviews.

Definitions

The following terms will be noted throughout this EAL project.

i. **Immunonutrition:** a nutrition intervention that is fortified with high doses of arginine, glutamine, omega-3 fatty acids and/or nucleotides that aims to modulate immune responses

ii. **Head and Neck Cancers:** cancers with origins in the oral cavity, pharynx, larynx, sinuses, nasal cavity, or salivary glands

iii. **Preoperative Phase:** any duration of time between the decision to undergo surgery and entering the operation room

iv. **Postoperative Phase:** any duration of time following the surgery; variable definition can range from days in the hospital to months of recovery

v. **Perioperative Phase:** encompasses the entirety of preoperative and postoperative phases

Summary

In general, cancer can interrupt metabolism and disturb a patient's nutritional status; However, head and neck cancers field additional issues, such as mechanical difficulties or dysphagia, that can lead to malnutrition as early as at diagnosis. With such a vulnerable population, it is crucial to continually analyze present care guidelines and improve them based on the most recent literature. Immunonutrition is a concept that has potential to make a difference in the surgical outcomes of head and neck cancer patients. Therefore, this evidence analysis project investigates the impact that immunonutrition implementation in the pre-, peri- and post-operative phases can have on the outcomes of patients undergoing head and neck cancer surgeries.

This evidence analysis project begins with a review of literature in chapter two. Then, it aims to answer the research question in chapter three by undergoing the five-step Evidence Analysis Process to assess the variety and quality of relevant studies on this topic. Finally, chapters four and five will review the results and discuss the outcomes and findings. Through this process, the goal is to reach a consensus on the most evidence-based, appropriate care

guidelines regarding the nutrition interventions in head and neck cancer surgical patients. Ideally, this will improve overall outcomes of surgery and has the potential to reduce malnutrition in this high-risk population.

Chapter 2: Review of the Literature

Cancer, a group of diseases characterized by the abnormal and rapid division of cells, has been the second leading cause of death in the United States (CDC, 2019). As this group of diseases have become increasingly prevalent over the decades, researchers have diligently worked to provide crucial insight into the causes and treatments of cancers. For example, carcinogenic compounds are continually identified, the efficacy of treatment drugs are being reviewed, and management of side effects is being fine-tuned. However, as is common in the medical field, researchers continue to work toward quality improvement in treating, and potentially curing, cancer diagnoses.

Background

Part of this improvement process includes investigating nutrition, specifically the nutrition implications of cancer. It has been well-supported that oncology patients are hypermetabolic and have elevated needs for calories and protein in the diet. According to ESPEN guidelines, calorie needs are often elevated to 25-30 calories per kilogram of body weight and protein needs are often estimated at 1.2-1.5 grams per kilogram of body weight (Arends, et al., 2016). With these guidelines and the understanding of the importance of nutrition, it is crucial to focus on nutrition interventions that provide the most optimal nourishment for the treatment of cancer.

Immunonutrition

In the presence of stress, the human body can produce a systemic inflammatory response in an effort to protect and heal (Brody, n.d.). As Brody further explains, when foreign antigens are involved, such as bacteria or viruses, the body elicits an immune response through a series of hormone signaling cascades. In these situations, B cells attack intruders by creating antibodies. T

lymphocytes, also known as T cells, are a type of white blood cell that is tasked with attacking host cells that have been invaded or are cancerous and regulating the immune response by activating other immune cells (Brody, n.d.). Malnutrition is known to interfere with the body's ability to fight and defend itself by impairing T cell function. Depending on the severity of the malnutrition and stressor, significant complications can arise such as localized infection, systemic sepsis, or even death.

Certain medical interventions can be implemented with the purpose of preventing or reducing these complications and improving outcomes for the patient. The term "immunonutrition" refers to a nutrition intervention with high doses of specific nutrients that aim to modulate these immune responses (Mauskopf et al., 2012). Immune-modulating products can be for oral, parenteral, or enteral use. The purpose of this literature review is to assess the role of immunonutrition, specifically including arginine, glutamine, ribonucleic acids and n-3 fatty acids, in the outcomes of cancer patients undergoing treatment. More specifically, this literature review will lend clarity to appropriate immunonutrition interventions in head and neck cancer patients undergoing surgical intervention.

To conduct this literature review, a search strategy was implemented. The collection of articles included all original research and meta-analyses regarding immunonutrition implementation in the head and neck surgical oncology population. Inclusion criteria entailed research within the last 20 years (2000 or later) for randomized control trials or written in the last 20 years (2000 or later) for meta-analyses and reviews. The meta-analyses and reviews could include research greater than 20 years old. Exclusions of this search plan include cancers outside of the head and neck regions and research outside of the aforementioned timeframes. The literature review was conducted utilizing several databases, including PubMed, SpringerOpen,

Cochrane Review, and Biomed Central. Search terms included: “immunonutrition head and neck cancer,” “immunonutrition head and neck surgery,” “arginine head and neck cancer,” “glutamine head and neck cancer,” “omega-3 fatty acids head and neck cancer,” and “nucleotides head and neck cancer.”

Immune-Modulating Nutrients

Many nutrients are thought to impact the human immune response, whether as protagonists of healing, antagonists of inflammation, or both. There is ongoing research to determine the full effects of these “immunonutrients.” Presently, four of the more commonly studied “immunonutrients” include arginine, glutamine, nucleotides/ribonucleic acids and n-3 fatty acids.

Arginine

As with many amino acids, arginine is quite versatile in its roles throughout the body. It serves as a precursor of polyamines, nucleic acids, and other amino acids and it can also promote secretion of prolactin and insulin in the body (Calder, 2003). However, some of the most important roles of arginine relate to its impact as an immunonutrient. Arginine is considered a conditionally essential amino acid, meaning the human body can typically produce enough of this amino acid to not require it from food intake. However, in atypical situations such as significant illness or trauma, the body’s endogenous production can be reduced, and the present stores may not be adequate enough for healing (Felekis et al., 2010). For example, arginine concentrations in the blood are lower in oncology patients, suggesting a possible shift in arginine metabolism in this catabolic state (Buijs et al, 2010). Arginine has been associated with preventing infection, reducing inflammation, and promoting healing (Vidal-Casariego et al., 2014). Therefore, in catabolic situations, exogenous supplementation of arginine in the diet

above standard estimated requirement can become crucial to immune functions of the body (Wu et al., 2019).

One of the most well-researched aspects of arginine is its role in preventing infection. In conjunction with nitric oxide synthase, arginine produces nitric oxide, which is pertinent in the immune response (Tripathi et al., 2007). Of significant importance is the ability of this nitric oxide substrate to regulate immune cells such as the T lymphocytes (Tripathi et al., 2007). As aforementioned, T cells can also target host cells that have become cancerous. By moderating T cells amidst bodily stress, arginine becomes essential to distinguishing and extinguishing infectious threats. As previously discussed, there is an unfortunate disruption in arginine metabolism in the context of cancer, exhibited by lower plasma arginine levels in cancer patients (Buijs et al., 2010). This further emphasizes the potential benefits of arginine supplementation in this metabolically stressed population.

In critical stress, inflammation of an area classically manifests in swelling, redness, and warmth. This is a result of vasodilation promoting blood flow to the affected area. Arginine-derived nitric oxide serves as a vasodilator, allowing this inflammatory process to proceed; therefore, arginine can significantly modulate inflammation in the body (Mayo Clinic Staff, 2017). In the context of oncology populations, arginine becomes critical for managing the ongoing inflammation throughout these metabolically stressed patients.

An additional immune-modulating characteristic of arginine is its role in wound healing. Increased plasma levels of arginine have been associated with growth hormone production, and therefore increased production of collagen (Pierre et al., 2013). This combination enhances the body's ability to repair wounds, which is especially important following surgery or trauma, especially in the presence of malnutrition.

Glutamine

Similar to arginine, glutamine is also an immune-modulating amino acid that is pertinent to the body's inflammatory response and healing. It, too, is a precursor for amino acids and nucleotides, such as arginine, in the body's standard physiology (Calder, 2003). Glutamine is nonessential and quite prevalent in a healthy body; It is the most abundant amino acid throughout the body with concentrations at 500-900 μmol/L (Pierre et al., 2013). However, in a highly catabolic state, the body's demands for glutamine can be in excess of its production and glutamine becomes conditionally essential. If glutamine stores are in deficit, it can cause further exacerbation of malnutrition and inflammation (Kim, 2011). Thus, when these high demands during metabolic stress outweigh the endogenous production, exogenous supplementation could benefit the physiologic immune process. When appropriate levels of supplementation are achieved, glutamine can provide adequate energy to immune cells, maintain cellular immune functions, and protect the intestinal mucosa from being damaged.

As aforementioned, T cells and B cells are responsible for defending the body from viruses, bacteria, and toxins. Amidst the body's immune response, glutamine serves as metabolic fuel for a variety of immune cells, namely these two varieties of lymphocytes (Ma et al., 2018). Therefore, it can be said that glutamine maintains cellular immune function and in the contexts of critical care and oncology, glutamine maintains an important role in fueling these essential white blood cells. In addition to enhancing the immune response, glutamine also helps to suppress pro-inflammatory signaling pathways by inhibiting production of cytokines (Kim, 2011). This creates a situation where a critically stressed body has reduced inflammation paired with an enhanced ability to combat what inflammation does remain. In the oncology population,

this can equate to drastically improved outcomes throughout the system as a whole, as well as in particularly inflamed areas.

Glutamine holds significant importance in the intestine, specifically in protecting the intestinal mucosa. The intestine utilizes around 30% of all glutamine, as glutamine is the energy source of choice for intestinal enterocytes that are constantly undergoing proliferation (Kim & Kim, 2017). This proliferation is also impacted by glutamine-moderated growth factors, specifically epidermal growth factor and insulin growth factor-I. Because glutamine is so closely involved in proliferation, it is also responsible for the maintenance of tight junctions in the intestine. It can protect against intestinal injury and improve the effectiveness of the gut barrier, especially amidst damage caused by chemotherapy or radiation treatment, of which most head and neck surgical patients undergo (Yavas et al., 2019). Thus, appropriate stores of glutamine are essential for preventing intestinal permeability and protecting the intestinal barrier (Kim and Kim, 2017).

Nucleotides

Nucleotides are another variety of immunonutrients commonly found in immune-modulating formulas. Nucleotides are the building blocks of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). Therefore, nucleotides as an ingredient in immunonutrition formulas are often referred to as RNA, as this is simply a long polymeric chain of nucleotides. In highly catabolic situations such as trauma, injury, and infection, the body's requirements for nucleotides is significantly elevated secondary to the increased need for immune cells (Bianchini et al., 2012).

Nucleotides can play an important role in catabolic states, as it is pertinent to immune cell proliferation and regulation. Specifically, there is a notable decrease in T-helper lymphocytes and

reduced production of interleukin-2 amidst depletion of nucleotides in catabolic states (Bianchini et al., 2012). T-helper lymphocytes are necessary for activation of B cells and T cells in the immune response. Interleukin (IL) -2 is responsible for regulating white blood cells in the immune response. Therefore, nucleotides serve a significant role in modulating the immune response following injury or trauma and restoring the immune system during the recovery period (Bianchini et al., 2012).

Also pertinent to the recovery process, it has been found that nucleotide supplementation can positively impact protein synthesis and therefore wound healing (Felekis, et al., 2010). As with all physiologic processes, energy is required for wound healing. Another role of nucleotides in the body is as chemical energy to fuel metabolism (Calder, 2007). Adenosine triphosphate, a nucleotide, is the physiologic currency for energy in the body. Not only is it utilized in energy transfer, but it is also a crucial coenzyme for numerous biological reactions, including healing and immune responses to catabolic situations (Bowater & Gates, 2015). Therefore, adequate supplementation during times of high nucleotide demand is essential for continuing the protein synthesis, wound healing and immune response processes.

Omega-3 Fatty Acids

Omega-3 fatty acids (also known as n-3 fatty acids) are a family of polyunsaturated fats that have been widely researched for decades. There are three varieties of omega-3 fatty acids: α-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). ALA is most commonly found in plant oils, while EPA and DHA are commonly found in marine oils or fortified food sources, such as eggs (National Institute of Health, 2020). Although these are prevalent in a variety of food sources, many people opt for additional omega-3 in the form of supplementation. For patients who could benefit from immunonutrition, omega-3 fatty acids are

common to oral and enteral immune-modulating formulas. However, it has also been found that appropriate balance between n-6 and n-3 fatty acids in parenteral nutrition formulations can impact immune function (Bianchini et al., 2012).

Similar to the immunonutrients previously discussed, omega-3 fatty acids have also been shown to have immune-modulating effects in situations of extreme bodily stress. Specifically, it is known that n-3 fatty acids contribute anti-inflammatory properties by modulating the gene expression of inflammatory cytokines, eicosanoids, chemokines, adhesion molecules, platelet activating factor, and reactive oxygen and nitrogen species. It is also noted that this nutrient positively increases anti-inflammatory cytokines (Wu et al., 2019).

As was established with arginine and glutamine, leukocytes are also impacted by the effects of omega-3 fatty acids. These fatty acids are known to change the activation process for antigen presenting cells (APCs), which in turn affect the T cell receptors. In a more direct manner, omega-3 fatty acids can act directly on T cells and have been generally found to suppress their function (Gutierrez et al., 2019). Correlations between B cells and omega-3 fatty acids are not as clearly defined in research. Although most research suggests a reduction in B cell activation by polyunsaturated fatty acids, Gutierrez et al. (2019) report controversy throughout the present literature. This inhibition of inflammatory reactions has specifically been noted amongst several cancer diagnoses, including head and neck varieties (Hanai et al., 2018).

Immunonutrition Products

A variety of immunonutrition products have reached the market, both in oral and enteral formulations. Each product includes a proprietary combination of immunonutrients, commonly including arginine, glutamine, nucleotides, and/or omega-3 fatty acids. The following are two

examples of mainstream immunonutrition products available on the market today: Nestle's IMPACT® and Abbott's Ensure Surgery®.

Nestle's IMPACT Advanced Recovery®

IMPACT Advanced Recovery® includes a blend of dietary nucleotides, arginine, and omega-3 fatty acids. The claims associated with the product include supported post-operative recovery, reduced infection risk, and reduced length of stay (Nestle, n.d.). Each carton in 6 ounces (178 mL) and comes in vanilla flavor. In addition to the nutrients listed in Table 1, a blend of vitamins and minerals are also included.

Table 1.

IMPACT Advanced Recovery® Composition.

Nutrient	Amount (per 8 ounce serving)
Protein, g	18
L-Arginine, g	4.2
Omega-3 (EPA + DHA), g	1.1
Dietary Nucleotides, mg	430
Carbohydrates, g	15
Calories	200

(Nestle, n.d.)

Abbott's Ensure® Surgery

Ensure® Surgery Immunonutrition Shake is an oral nutrition drink that is fortified with immune-supporting ingredients. The claims associated with the product include enhanced immune health, protein synthesis, tissue repair, and wound healing (Abbott, n.d.). Each carton is

8 ounces (237 mL) and comes in vanilla flavor only. In addition to the nutrients listed in Table 2, a blend of vitamins and minerals are also included.

Table 2.

Ensure® Surgery Composition.

Nutrient	Amount (per 8 ounce serving)
Protein, g	18
L-Arginine, g	4.2
Omega-3 (EPA + DHA), g	1.1
Carbohydrates, g	45
Calories	330

(Abbott, n.d.)

Immunonutrition Applications

Immunonutrition can be applied to many medical conditions, but research surrounding immune-modulating formulas is particularly strong in oncology populations. Due to the many side effects and complications of oncologic treatment, the immune system plays an immense role in this population.

General Oncology

As previously discussed, oncology patients are hypermetabolic at baseline and immunonutrition interventions have significant importance in catabolic situations to promote healing, prevent complications, and modulate immune responses. Therefore, when oncologic plans of care involve intensive chemotherapy, radiation therapy and/or surgical interventions, it is important to consider the addition of immune-modulating formulas to balance catabolic breakdown of tissues and muscle mass.

Oncology Research and Immunonutrition. Chemotherapy and radiation therapy pose a strong potential for side effects from treatment. These side effects depend greatly on the dosing of chemotherapy and/or the target location of the radiation therapy. For example, radiation to the head and neck region will likely result in mucositis and mechanically difficulty when eating. On the other hand, systemic chemotherapy may have a broader scope of impact, such as generalized nausea and fatigue. Research has been focused on these issues and symptom management. For example, L-Glutamine has been studied as a naturopathic supplement in treating and preventing mucositis and cachexia that is common among all oncologic diagnoses (Noe, 2009).

In addition to symptom management, immunonutrition could also play a role in cancer growth and advancement. Despite controversy regarding desirability of L-Glutamine to malignant cells, research has demonstrated preferential uptake of L-Glutamine by non-cancerous cells, resulting in reduced cancer growth (Noe, 2009). These results are promising across cancer in general, but further research has been conducted with specific cancer types.

As previously discussed, several immunonutrients play a role in tissue proliferation and wound healing, which is essential in mitigating post-operative complications. Studies compiled in one meta-analysis found that immunonutrition can reduce infectious complications after surgical resection (Buzquurz et al., 2020). As a result of these findings, the researchers concluded that oral immune-modulating nutrition supplementation should be considered, as reported side effects of implementation were minimal across all studies. Additionally, the comparative cost of immunonutrition implementation versus the cost of complications speaks in favor of the proactive approach (Mauskopf et al, 2012). Further research investigating the appropriate timing of immunonutrition has been, for the most part, diagnosis specific.

Gastrointestinal Cancer

Gastrointestinal cancers often entail complex treatment courses, frequently with the curative treatment option being surgical intervention. Those with gastrointestinal cancer diagnoses face a significantly higher post-surgical complication rate between 15% and 54% (Mauskopf et al., 2012). Immunonutrition can be implemented prior to surgery, following surgery, or both. In the meta-analysis conducted by Song et al. (2015), researchers found that postoperative immunonutrition was ideal for preventing noninfectious complications. However, perioperative intervention appeared optimal in regard to postoperative infectious complications and length of stay. Accordingly, researchers concluded that immunonutrition implemented perioperatively exhibited preferable results compared to standard formulas and preoperatively or postoperatively alone (Song et al., 2015).

Considering the elevated per patient cost with this high-risk population, immunonutrition has been investigated as a means for mitigating this costly complication rate. Mauskopf et al. (2012), evaluated the effect of perioperative immunonutrition on the hospital costs of gastrointestinal cancer surgical candidates. The researchers found per patient savings of $3300 were noted due to reduced infectious complications with immunonutrition present. In regard to reducing length of stay in the hospital, per patient savings of $6000 USD were found. With these values in mind, the researchers concluded that immunonutrition is a relatively inexpensive investment in preventing severe complications and elevated costs in gastrointestinal cancer surgery patients (Mauskopf et al., 2012).

Head and Neck Cancers

Head and neck cancers are another group of oncologic diagnoses that are prevalent in the immunonutrition literature, due to the immense nutrition impact felt by these patients. In 2020,

there were 53,260 new diagnoses of head and neck cancer in the United States, making up approximately 2.95% of all cancer diagnoses (American Cancer Society, 2020). Individuals with these diagnoses commonly undergo a variety of treatment interventions, including surgery, chemotherapy, radiation, or concurrent chemoradiation. Because these interventions induce significant inflammation, concurrent treatments often result in severe side effects. Due to the location of the treatment site, negative nutrition implications are very common. Immunonutrition before and throughout chemoradiation has been studied to assess for possible reduction of inflammation and prevention of severe mucositis. A study by Machon et al. (2012), investigated these proposed effects of immunonutrition on inflammation. The researchers found that some markers of inflammation were decreased in the presence of immunonutrition and there was a lower incidence of severe mucositis noted. Thus, oral immunonutrition in concurrent treatment for head and neck cancers may be a means to improve biochemical and physical outcomes for patients (Machon et al., 2012).

Aside from inflammation, head and neck cancers pose a unique nutrition situation if surgery induces an anatomical change of mouth and throat, making oral intake difficult for the patient. According to De Luis et al. (2013), up to 35-50% of individuals with head and neck cancer are in a significantly malnourished state and require complex nutritional interventions by the care team (De Luis et al, 2013). Throughout treatment and especially leading into surgery, this malnutrition can pose several issues with healing and recovery. Following surgery, malnutrition can contribute to severe complications, including infection. According to Buzquurz et al. (2020), infectious complications were found in 4-22 percent of patients that underwent a surgical resection of a malignant solid tumor (Buzquurz et al, 2020). The use of immunonutrition to counteract this high incidence rate has been studied extensively in surgical patients undergoing

resection for head and neck cancer diagnoses. Notable increases in immune cells and decreases in post-operative complications have been found (Sorensen et al, 2009). Although these results are promising, many studies have been conducted on small sample sizes, which will require additional investigation to confirm.

Research Methodology

The current literature discussed throughout this review suggests immunonutrition, including arginine, glutamine, nucleotides, and omega-3, could be a beneficial intervention in this specific population as these nutrients serve important roles in enhancing recovery after surgical intervention (Smith et al., 2020). Although there is evidence in the literature, there is currently no definitive guideline for clinicians on the use of immunonutrition in the operative phases for head and neck cancer surgery patients, making an EAL project the most appropriate apporach. It is important to develop a consensus on this topic to provide consistency and utmost efficacy in patient care. The following chapters will work toward a concrete, evidence-based recommendation regarding the use of immunonutrition in the head and neck cancer surgical population.

Conclusion

It is the ethical responsibility of clinicians, doctors and dietitians alike, to investigate alternative treatments that promote the best outcomes for all patients, especially those in highly metabolic, stress-ridden states. In this regard, there is an exceptional need among patients undergoing head and neck cancer surgery. The next chapter outlines the methodology behind the Evidence Analysis Project that will investigate this need.

Chapter 3: Methodology

The methodology of this evidence analysis project is based on the five-part Evidence Analysis Process that was designed and outlined by the Academy of Nutrition and Dietetics. Through this process, present literature on a topic is critically evaluated to reach a consensus that will optimize the practice of nutrition professionals (Academy of Nutrition and Dietetics, 2016). For this project, the process was implemented to investigate the current research on implementation of immunonutrition in head and neck cancer patients undergoing surgery. Each of the five steps is outlined below as it pertains to the research question at hand.

Evidence Analysis Process

Step One: Formulate the Evidence Analysis Question

According to the Evidence Analysis Manual, a strong evidence analysis question assesses current research on a topic against the remaining gaps in literature (Academy of Nutrition and Dietetics, 2016). Prior to formulating the question, a good question must take into account key factors of the Nutrition Care Process (NCP) that can impact outcomes and any links between factors of the NCP. Once all factors have been evaluated, the Evidence Analysis Process encourages use of the PICO format to develop the research question. PICO breaks down into four components: the population, the intervention(s), the comparison, and the outcome(s) of interest. Table 3 demonstrates this format.

Table 3.

PICO Format.

Component	Definition
Population	Adult patients undergoing surgical intervention for head and neck cancer
Intervention	Immunonutrition in the pre, post, and perioperative periods of surgery
Comparison	Standard, non-immunofortified intake
Outcome of Interest	Prevalence of any post-operative complications, including infection, sepsis, death

(Academy of Nutrition and Dietetics, 2016).

As a result of PICO formatting, the evidence analysis question is: Does implementation of immunonutrition in the pre-, peri- and/or post-operative phase reduce complications and improve outcomes for adult patients undergoing surgical intervention for head and neck cancer? Steps two through five of the Evidence Analysis Process will be conducted based on this research question.

Step Two: Gather and Classify the Evidence

In the second step of the Evidence Analysis Process, a search plan was designed to collect articles/evidence through appropriate databases and specified search terms. Once the search was conducted based on the search plan, all articles were reviewed to filter through the studies based on inclusion and exclusion criteria outlined in the search plan. Documentation of the search plan and the filtered articles was compiled into the Search Plan and Results found in Table 4.

Table 4.

Search Plan and Results.

Question

Does implementation of immunonutrition in the pre-, peri- and/or post-operative phase reduce complications and improve outcomes for adult patients undergoing surgical intervention for head and neck cancer?

Date of Literature Review for the Evidence Analysis

2020

Inclusion Criteria

- Adult subjects
- Research within the last 20 years (2000 or later) for randomized control trials or written in the last 20 years (2000 or later) for meta-analyses and reviews
    - Meta-analyses and reviews can include research > 20 years old

Exclusion Criteria

- Pediatric subjects
- Research based on cancers outside of the head and neck regions
- Study size: <15 participants in either study group (intervention or control)
- Research outside of the following timeframes
    - Research within the last 20 years (2000 or later) for randomized control trials
    - Written in the last 20 years (2000 or later) for meta-analyses and reviews

Search Terms

- "immunonutrition head and neck cancer"
- "immunonutrition head and neck surgery"
- "arginine head and neck cancer"
- "glutamine head and neck cancer"
- "omega-3 fatty acids head and neck cancer"
- "nucleotides head and neck cancer"

Electronic Database Used

- PubMed (filtered to only include articles within the last 20 years)

Articles to Review:

- immunonutrition head and neck cancer → 51 articles
- immunonutrition head and neck surgery → 9 articles
- arginine head and neck cancer → 278 articles
- glutamine head and neck cancer → 139 articles
- omega-3 fatty acids head and neck cancer → 73 articles
- nucleotides head and neck cancer → 4434 articles

Articles Included:

Azman, M., Mohd Yunus, M. R., Sulaiman, S., & Syed Omar, S. N. (2015). Enteral glutamine supplementation in surgical patients with head and neck malignancy: A randomized controlled trial. *Head & Neck, 37*(12), 1799–1807. https://doi.org/10.1002/hed.23839

Barajas-Galindo, D. E., Vidal-Casariego, A., Pintor-de la Maza, B., Fernandez-Martinez, P., Ramos-Martinez, T., Garcia-Arias, S., Hernandez-Moreno, A., Urioste-Fondo, A.,

Cano-Rodriguez, I. & Ballesteros-Pomar, M. D. (2019). Postoperative enteral immunonutrition in head and neck cancer patients: Impact on clinical outcomes. *Endocrinologia, Diabetes y Nutricion, 67*(1), 13-19. doi:10.1016/j.endinu.2019.05.006

Buijs, N., Van Bokhorst-de van der Schueren, M. A., Langius, J., Leemans, C. R., Kuik, D. J., Vermeulen, M., & Van Leeuwen, P. (2010). Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival. *American Journal of Clinical Nutrition,* 92, 1151-1156. doi:10.3945/ajcn.2010.29532

De Luis, D., Izaola, O., Cuellar, L., Terroba, M., Ventosa, M., Martin, T., & Aller, R. (2013). Clinical effects of a w3 enhanced powdered nutritional formula in postsurgical ambulatory head and neck cancer patients. *Nutricion Hospitalaria, 28*, 1463-1467. doi:10.3305/nh.2013.28.5.6662

Falewee, M., Schilf, A., Boufflers, E., Cartier, C., Bachmann, P., Pressoir, M., Banal, A., Michel, C., & Ettaiche, M. (2013). Reduced infections with perioperative immunonutrition in head and neck cancer: Exploratory results of a multicenter, prospective, randomized, double-blind study. *Clinical Nutrition, 33*, 776-784. doi:10.1016/j.clnu.2013.10.006

Mueller, S. A., Mayer, C., Bojaxhiu, B., Aeberhard, C., Schuetz, P., Stanga, Z., & Giger, R. (2019). Effect of preoperative immunonutrition on complications after salvage surgery in head and neck cancer. *Journal of Otolaryngology - Head & Neck Surgry, 48*(25), 1-9. doi:10.1186/s40463-019-0345-8

Vidal-Casariego, A., Calleja-Fernandez, A., Villar-Taibo, R., Kyriakos, G., Ballesteros-Pomar, & D, M. (2014). Efficacy of arginine-enriched enteral formulas in the reduction of surgical complications in head and neck cancer: A systematic review and meta-analysis. *Clinical Nutrition, 33*, 951-957. doi:10.1016/j.clnu.2014.04.020

Excluded Articles

Article	**Reason for Exclusion**
Buzquurz, F., Bojesen, R., Grube, C., Madsen, M., & Gogenur, I. (2020). Impact of oral preoperative and perioperative immunonutrition on postoperative infection and mortality in patients undergoing cancer surgery: systematic review	Type of disease (non-specific, general oncology diagnosis)

and meta-analysis with trial sequential analysis. *BJS Open, 4*, 764-775. doi:10.1002/bjs5.50314	
Felekis, D., Eleftheriadou, A., Papadakos, G., Bosinakou, I., Ferekidou, E., Kandiloros, D., Katsaragakis, S., Charalabopoulos, K., & Manolopoulos, L. (2010). Effect of Perioperative Immuno-Enhanced Enteral Nutrition on Inflammatory Response, Nutritional Status, and Outcomes in Head and Neck Cancer Patients Undergoing Major Surgery. *Nutrition and Cancer, 62*(8), 1105-1112. doi:10.1080/01635581.2010.494336	One of study groups with n < 15
Hanai, N., Terada, H., Hirakawa, H., Suzuki, H., Nishikawa, D., Beppu, S., & Hasegawa, Y. (2018). Prospective randomized investigation implementing immunonutritional therapy using a nutritional supplement with a high blend ratio of w-3 fatty acids during the perioperative period for head and neck carcinomas. *Japanese Journal of Clinical Oncology, 48*(4), 356-361. doi:10.1093/jjco/hyy008	Control group and intervention group each with n < 15
Kim, M.-H., & Kim, H. (2017). The Roles of Glutamine in the Intestine and Its Implication in Intestinal Disease. *International Journal of Molecular Sciences, 18*(1051). doi:10.3390/ijms18051051	Type of disease (Intestinal)
Machon, C., Thezenas, S., Dupuy, A.-M., Assenat, E., Michel, F., Mas, E., Senesse, P., & Cristol, J.-P. (2012). Immunonutrition before and during radiochemotherapy: improvement of inflammatory parameters in head and neck cancer patients. *Support Care Cancer, 20*, 3129-3135. doi:10.1007/s00520-012-1444-5	Type of treatment (non-surgical)
Mauskopf, J. A., Candrilli, S. D., Chevrou-Severac, H., & Ochoa, J. B. (2012). Immunonutrition for patients undergoing elective surgery for gastrointenstinal cancer:	Type of disease (Gastrointestinal cancer)

impact on hospital costs. *World Journal of Surgical Oncology, 10*(136), 1-7.	
Ma, C., Tsai, H., Su, W., Sun, L., Shih, Y., & Wang, J. (2018). Combination of arginine, glutamine, and omega-3 fatty acid supplements for perioperative enteral nutrition in surgical patients with gastric adenocarcinoma or gastointestinal stromal tumor (GIST): A prospective, randomized, double-blind study. *Journal of Postgraduate Medicine, 64*, 155-163. doi:10.4103/jpgm.JPGM_693_17	Type of disease (Gastrointestinal cancer)
Smith Jr, T. W., Wang, X., Singer, M. A., & Godellas, C. V. (2020). Enhanced recovery after surgery: A clinical review of implementation across multiple surgery subspecialties. *The American Journal of Surgery, 219*, 530-534. doi:10.1016/j.amjsurgery.2019.11.009	Type of disease (non-specific)
Song, G.-M., Tian, X., Zhang, L., Ou, Y.-X., Yi, L.-J., Shuai, T., Zhou, J.-G., Zeng, Z, & Yang, H.-L. (2015, July). Immunonutrition Support for Patients Undergoing Surgery for Gastrointestinal Malignancy: Preoperative, Postoperative, or Perioperative? A Bayesian Network Meta-Analysis of Randomized Controlled Trials. *Medicine, 94*(29), 1-17. doi:10.1097/MD.0000000000001225	Type of disease (Gastrointestinal)
Sorensen, D., McCarthy, M., Baumgartner, B., & Demars, S. (2009). Perioperative Immunonutrition in Head and Neck Cancer. *The Laryngoscope, 119*, 1358-1364. doi:10.1002/lary.20494	Control group and intervention group each with n < 15
Turnock, A., Calder, P. C., West, A. L., Izzard, M., Morton, R. P., & Plank, L. D. (2013). Perioperative Immunonutrition in Well-Nourished Patients Undergoing Surgery for Head and Neck Cancer: Evaluation of Inflammatory and	Control group and intervention group each with n < 15

Immunologic Outcomes. *Nutrients, 5*, 1186-1199. doi:10.3390/nu5041186	
Yavas, C., Yavas, G., Celik, E., Buyukyoruk, A., Buyukyoruk, C., Yuce, D., & Ata, O. (2019). Beta-Hydroxy-Beta-Methyl-Buytrate, L-glutamine, and L-arginine Supplementation Improves Radiation-Induce Acute Intestinal Toxicity. *Journal of Dietary Supplements, 16*(5), 576-591. doi:10.1080/19390211.2018.1472709	Type of treatment (non-surgical)

Step Three: Critically Appraise Each Article

The third step outlined by the Evidence Analysis Process is to review each article and abstract the most pertinent points onto a worksheet or using the Data Extraction Tool. These tools allow for easier comparison between studies, as all key information (for example, major findings, limitations, and study quality) is consistently recorded. For this EAL project, the Evidence Abstract Worksheet (Appendix 1) will be used to organize the articles in a uniform manner. Then, the Quality Criteria Checklist (Appendix 1) will be completed for each to assess the applicability to practice and the validity, which helps to determine the overall rating of each study. The final rating can be positive (+), neutral (∅) or negative (-) and will be assigned on the Evidence Worksheet. Finally, all information from this critical appraisal of articles will be combined into a summary table of checklists (Appendix 1), allowing for quick comparison and review.

Step Four: Summarize the Evidence

In the Evidence Analysis Process, step four entails developing a coherent, straight-forward summary of the pertinent and valid evidence found. The EAL Manual refers to this summary as “a status of the science conclusion” (Academy of Nutrition and Dietetics, 2016).

The EAL Process describes two methods of summarizing the evidence: the Worksheet Overview Table and the Evidence Summary. The Overview Table (Figure 1) is used to analyze the most pertinent studies for the Evidence Analysis Question at hand.

Figure 1.

Evidence Overview Table.

Author, Year, Study Design, Class Rating	Study Type / Purpose	Study Populations	Intervention	Outcomes	Limitations

(Academy of Nutrition and Dietetics, 2016).

Studies that are most valid and reliable, such as those with higher ratings or optimal sample sizing, will be more important to weigh in on the EAL Question than studies of lesser size or lower rating. Each relevant study will have a statement that discusses its pertinence to the EAL Question.

Once the Overview Table is complete, it is used to determine patterns and trends between the studies. According to the EAL Manual, there are five key components of the Evidence Summary:

1. An overall summary statement
2. Comparison factors statements
3. Methodological statements
4. Outcome impact statements
5. Definitions of key terms

These five components are expected to be included to have a well-rounded summary narrative in the Evidence Analysis Process.

Step Five: Write and Grade the Conclusion Statement

Finally, the fifth step of the process is to take all of the information collected throughout the prior four steps and grade the literature in order to develop a sound conclusion statement. The grading of this conclusion statement is dependent on the strength of the evidence available and is based on the Conclusion Grading Table that is provided by the EAL (Figure 2).

Figure 2.

Conclusion Grading Table.

Conclusion Grading Table					
Strength of Evidence Elements	**Grades**				
	I Good/Strong	**II Fair**	**III Limited/Weak**	**IV Expert Opinion Only**	**V Grade Not Assignable**
Quality • Scientific rigor/validity • Considers design and execution	Studies of strong design for question Free from design flaws, bias and execution problems	Studies of strong design for question with minor methodological concerns, OR Only studies of weaker study design for question	Studies of weak design for answering the question OR Inconclusive findings due to design flaws, bias or execution problems	No studies available Conclusion based on usual practice, expert consensus, clinical experience, opinion, or extrapolation from basic research	No evidence that pertains to question being addressed
Consistency Of findings across studies	Findings generally consistent in direction and size of effect or degree of association, and statistical significance with minor exceptions at most	Inconsistency among results of studies with strong design, OR Consistency with minor exceptions across studies of weaker design	Unexplained inconsistency among results from different studies OR single study unconfirmed by other studies	Conclusion supported solely by statements of informed nutrition or medical commentators	NA
Quantity • Number of studies • Number of subjects in studies	One to several good quality studies Large number of subjects studied Studies with negative results have sufficiently large sample size for adequate statistical power	Several studies by independent investigators Doubts about adequacy of sample size to avoid Type I and Type II error	Limited number of studies Low number of subjects studied and/or inadequate sample size within studies	Unsubstantiated by published research studies	Relevant studies have not been done
Clinical impact • Importance of studied outcomes • Magnitude of effect	Studied outcome relates directly to the question Size of effect is clinically meaningful Significant (statistical) difference is large	Some doubt about the statistical or clinical significance of the effect	Studied outcome is an intermediate outcome or surrogate for the true outcome of interest OR Size of effect is small or lacks statistical and/or clinical significance	Objective data unavailable	Indicates area for future research
Generalizability To population of interest	Studied population, intervention and outcomes are free from serious doubts about generalizability	Minor doubts about generalizability	Serious doubts about generalizability due to narrow or different study population, intervention or outcomes studied	Generalizability limited to scope of experience	NA

(Academy of Nutrition and Dietetics, 2016).

Next Steps

In the next chapter, the research studies included in this EAL will be reviewed in terms of results found. Then, a discussion chapter will entail a summary of the evidence, as well as the direction for future research.

Chapter 4: Results

Individuals with a head and neck cancer diagnosis may be nutritionally at-risk due to the tumor location and metabolic stress from the disease state. Treatment plans, including surgical intervention, can increase this nutritional risk significantly. Knowing the negative impact malnutrition has on oncologic outcomes, research has been investigating methods of improving nutrition status in patients, specifically head and neck cancer surgical candidates. This evidence analysis project evaluates the use of immunonutrition in surgical head and neck cancer populations as a means of mitigating nutritional risk. A total of seven research articles were included in this project, as outlined in the Search Plan and Results (Table 2). This chapter will review the results of the research studies that were included in the evidence analysis project in an effort to improve outcomes of head and neck cancer surgical candidates.

Study Analysis

Azman et al. (2015) – Quality Rating: Neutral

The prospective randomized clinical trial by Azman et al. (2015) aimed to evalute the post-operative effects of glutamine supplementation on head and neck cancer patients undergoing surgical intervention. The 44 recruited participants were randomized into the intervention and control groups using random ballot picking. Glutamine Plus was provided to the intervention group (n=22) via enteral access three times daily for the 4 weeks following surgery. Baseline (at first pre-operative visit) and post-intervention measurements were collected for fat-free mass, serum albumin, and quality of life scores. Significant findings were noted for the difference in serum albumin, fat-free mass, and quality of life scores between the intervention and control cohorts. Additionally, a significant correlation was found between the fat-free mass and quality of life of the sample patients. The authors therefore concluded that enteral glutamine

supplementation in this population may significantly improve the fat-free mass, serum albumin, and quality of life of these patients. Also, maintaining fat-free mass may improve post-operative quality of life scores in this population of patients.

This study had several strengths and limitations to be considered. One of the biggest strengths was that the sample was a moderate size for this population. In addition, the groups were homogenously distributed with no significant differences in demographics. The use of randomization of this sample strengthens the significant findings of improvement in lean body mass maintenance, serum albumin and quality of life. Qualty of life score was determined using a validated tool called the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. However, there were also some weaknesses that limited this study. The study design did not utilize blinding, which exposes the results to researcher bias. Additionally, the use of bioelectrial impedance analysis (BIA) as the measurement tool for body composition may be a potential limitation, as this technique does not take tumor mass into consideration. The researchers addressed these limitations and recommend future research use ultrasound techniques to prevent this limitation from impacting findings. One limitation that was not addressed by the authors was that the use of serum albumin is now known to not always ben indicative of nutrition status. Therefore, this limits the use of the albumin findings to inflammatory response, not the nutrition outcomes of the intervention.

Based on the statistical analysis and design of the study, the authors made appropriate conclusions. With further research to support these findings, clinical implementation of glutamine supplementation following head and neck surgery may be considered to improve postoperative outcomes of lean body mass, albumin, and quality of life.

Barajas-Galindo et al. (2019) – Quality Rating: Neutral

The retrospective observational study by Barajas-Galindo et al. (2019) was conducted for the purpose of determining whether enteral formulas enriched with arginine reduced the length of stay and fistula occurrence in postoperative head and neck cancer patients. This study included 135 patients who received postoperative nutrition support through a nasogastric tube between the timeframe of January 2012 and August 2018. Of the 135 total recruited participants, 68 patients received an immunonutriton formula that was enriched with arginine. The mean duration of postoperative tube feeding for this group was 19.12 days. In the early postoperative period, sociodemographic variables, anthropometrics, and nutrition interventions were recorded to compare groups. In addition, The outcomes of fistula occurrence, length of hospital stay, readmissions, and 90-day mortality rate were recorded. The researchers found a significantly lower rate of fistula occurrence and shorter average length of stay for the patients who received immunonutrition when compared to the standard formula. However, the significance of these findings was diminished when adjusting for age, energy intake, surgery complexity, and tumor staging. Although the intended primary outcomes were no longer significant after adjusting, the researchers did find a significant correlation between preoperative malnutrition and postoperative fistula incidence. This study was also able to investigate new information correlating malnutrition with postoperative fistula occurrence, considering over 88% of the patients were malnourished at operative admission. With this new evidence, there is more information supporting earlier nutrition intervention prior to surgical intervention.

When evaluating the study's efficacy, there are several strengths and limitations to consider. One of the key strengths was that the sample size was large compared to other studies on this topic. However, there were several limitations of the design, which the authors discussed

in detail. Foremost, this study was retrospective in nature which may have lead to discrepancies in care over time. The intervention group (immunonutrition recipients) were in a later time frame than the control group (standard nutrition); therefore, confounding variables such as team experience or changes in hospital policies could impact these results. Additionally, the authors did not ensure patients had met nutritional needs and thus a deficit was found between patient intake. Lastly, over two-thirds of the patients had carcinoma of the larynx, specifically, which limits the generalizability of the findings for all head and neck cancers. Given these limitations (which were acknowledged by the team), the conclusions drawn were appropriate for the information available. The implementation of an arginine-enriched enteral formula may reduce fistula occurrence and length of stay in this population, but it is dependent on age, tumor staging, and surgery complexity. However, a significant correlation between malnutrition and fistula occurrence suggests early nutrition intervention in the operative timeline may improve outcomes. The clinical impact of this article is limited, as additional research that is prospective in nature and accounts for nutritional needs of patients is essential to bringing these conclusions to practice.

Buijs et al. (2010) – Quality Rating: Neutral

The double-blinded, randomized control study by Buijs et al. (2010) analyzed the long-term effects of perioperative use of arginine supplementation in the severely malnourished head and neck cancer population. The long-term effects that were documented in follow-up included survival, recurrence, or new cancer. The study initially included 56 severely malnourished head and neck cancer patients, but the long-term follow-up included only 32 due to mortality. The participants were randomized into the control group (n=15) or intervention group (n=17), which received standard perioperative enteral nutrition or arginine-supplemented perioperative enteral

nutrition, respectively. The intervention enteral formula had 41% of its casein replaced by arginine, otherwise there were no other differences between the control and intervention formulas. Each patient had a target intake based on their actual body weight. Preoperatively, each patient received full nutrition via the tube feeding, but oral intake was also allowed. Postoperatively, the patients received the same product at the same volume target for 10 days following surgery until swallow study could be completed. If patients requried enteral nutrition beyond the 10 day timeframe, they were transitioned to the standard formulation. The primary outcome of interest was long-term survival, defined as 10 years postsurgery. Secondary outcomes that were measured included recurrence, distant metastases, or second primary tumor development. Based on these outcomes, the researchers found a significantly improved survival rate in the arginine-enriched group. Additionally, there was an improved disease-specific survival rate as well as locoregional recurrence survival. No statistically significant difference was found for the other outcomes of interest.

The design developed by Buijs et al. (2010) had important strengths and limitations to consider. This study was a significant contribution to this population because it investigated a cohort of patients over a long period of time (10 years). There are few studies in the present literature with this duration. Another strength was that it investigated the perioperative time frame, rather than just preoperative or postoperative. However, there were also some notable limitations, which the authors acknowledged. First, the sample size was small, with the final cohort for long-term follow-up having only 32 subjects. Because long-term follow-up is subject to mortality risk, a larger study initial sample size would be beneficial to add validity to the findings. Additionally, there were several confounding variables that were not accounted for, such as long-term diet, exercise, and smoking or drinking habits. These variables could be quite

influential over a 10-year span. The authors concluded that perioperative arginine-enriched nutrition may improve the long-term survival of head and neck cancer patients who present initially with malnutrition. This is an appropriate conclusion based on the study quality, however, further research is needed with larger cohorts of subjects and more consideration for confounding variables in order for these findings to impact clinical practice. With only this study in consideration, arginine-enriched immunonutrition could prove beneficial for clinical implementation, but the cost versus benefit balance is unknown.

De Luis et al. (2013) – Quality Rating: Neutral

The purpose of the prospective cohort study conducted by De Luis et al. (2013) was to investigate the effect of w3-enriched oral immunonutrition supplementation on nutritional and biochemical measures in the postoperative head and neck cancer population. This study included 33 patients with oral or laryngeal cancer that were post-surgical and ambulatory. Upon post-operative discharge, patients were instructed to take two units (50 g per unit) of the immunoenhanced powder formula (Resource Support Instant) per day for twelve weeks. At week 0, three day diet diaries, body weight and composition, bloodwork (albumin, prealbumin, transferrin) and enteral intolerance were recorded. Patients received follow up by a dietitian via phone every 14 days to improve monitoring. Following the twelve-week study period, the same diet diaries, labwork and anthropometric measurements were recorded. Three groups were assessed: the entire group (n=33), patients undergoing radiotherapy during intervention (n=15) and patients not undergoing radiotherapy during the intervention (n=18). There was a statistically significant improvement in blood protein concentration with the w-3 supplementation, as evidenced by albumin, prealbumin and transferrin lab values. In addition, weight, fat mass and

fat free mass were all improved with supplementation if the patient was not undergoing radiotherapy simultaneously.

A major strength of the protocol was the long duration of the intervention (95.9 day average). This three-month timeframe of supplementation is uncommon in the present literature. Alternatively, some limitations were noted but not by this study's authors themselves. As with several studies on this topic, there was a low overall sample size of 33 patients. Further research with a larger sample size would be necessary to improve validity of the findings. The design also lacked a true control group, which would improve future research including a larger population. Additionally, it is important to note that this study investigated the primary outcomes of serum protein concentrations, which are now known to not always be indicative of nutrition status. Therefore, these results may not be applicable in clinical nutrition practice, but the significant improvement in weight and body mass may impact nutrition practice pending further research.

Falewee et al. (2013) – Qualty Rating: Positive

The prospective, randomized, double-blinded study by Falewee et al. (2013) aimed to investigate whether immunonutiriton had the potential to reduce postoperative infectious complications, surgical-site infections, and/or length of stay. Additionally, the authors looked to assess the benefit of preoperative versus perioperative enteral nutrition. To do so, the authors recruited across eight medical centers to collect a total of 205 patients. Each participant had to have a diagnosis of SCC oral, oropharyngeal, laryngeal, or hypopharyngeal with the intent of surgical intervention. Baseline measurements were recorded between 30 days and eight days before surgery. These records included: oncologic and nutritional assessments, medical history, Karnofsky Performance Score, and risk factors. Participants were randomly dispersed between three groups: perioperative Impact without immune nutrients (Group A – control group),

preoperative Impact and postoperative standard diet (Group B), or perioperative Impact (Group C). The groups were found to be completely homogenous for demographic and clinical criteria. Patients were stratified according to their nutritional status. Each group received 1000 kcal/day from their respective formula preoperatively, and 1500 kcal/day postopertively. For the seven days prior to surgery, patients were given three doses of their allocated regimen. If the participant was malnourished upon beginning the study, enteral nutrition was initiated based on their allocated group regimen. Following surgery, enteral nutrition was administered for 7-15 days according to each participant's allocated regimen. The immunonutrition intervention groups received three feedings of Impact, and additional calorie and protein needs were met with the institution's standard nutrition protocol. The day before surgery, the subjects were weighed and evaulated for compliance with preoperative nutrition regimen. Patients were followed for 90-days following surgery. Within these three months, seven incremental follow-up appointments were arranged. At said appointments, the Karnofsky Performance Score, nutritional assessment (including anthropometrics), albumin level, and adverse events were recorded.

Overall, the authors did not find significant differences between the groups for the primary outcome of infection nor the secondary outcome of surgical site infection. Additionally, there was no significant difference in the average length of stay. It is important to note that the per protocol population was comprised of only 64 patients that had a compliance ratio between 75-100%. When evaluating the per protocol population alone, there was a significant difference in surgical site infections between group A and group C. This exhibited that compliance within this population is essential to gleaning the benefits from immunonutrition.

One strength of this study was that it was a multicenter study with an initially high sample size. In addition, the intervention and control groups were randomized, stratified for

nutrition status, and found to be homogenous on all other measured characteristics. Therefore, this study was developed for success. However, a large weakness of this study is that the lack of compliance by the patients resulted in a reduced sample size and interfered with the quality study design. The recruitment process was discontinued prior to reaching goal size of 420 participants due to low rate of enrollment and compliance. The authors of this study adequately addressed the limitations that occurred in this study. Although they were unable to achieve the results desired, they acknowledged that this same compliance issue has been prevalent in the literature across other studies. The conclusion reached was that the small per protocol population showed promising trends suggesting immunonutrition may reduce risk of infection, and therefore length of stay. However, the clinical impact of this study cannot be determined until larger studies with improved compliance are conducted.

Mueller et al. (2019) – Quality Rating: Neutral

The single-armed study by Mueller et al. (2019) used a historical cohort to investigate if preoperative immunonutrition can decrease complications of surgery for head and neck cancer patients. A total of 96 participants were included in the study based on their diagnosis of recurrent/persistent or second primary head and neck cancer after undergoing radiation, chemoradiation, or radiation with immunotherapy with curative intent. Diagnoses spanned across the head and neck region, including the oral cavity, oropharynx, hypopharynx and larynx. There were a total of 51 patients who received Nestle's Impact® immunonutrition, of which 41 received it orally and 10 received via a preexisting percutaneous endoscopic gastrostomy tube. Each subject in this intervention group received 3 units of Impact per day for 5 days prior to surgery. The remaining 45 patients included were the historical control group, and received standard nutrition. There were no statistically significant differences in demographics found

between the two groups. Prior to surgery, preoperative BMI and nutrition status were recorded using the Nutritional Risk Screening 2002 scoring. This scoring system accounts for weight loss, BMI, food intake, severity of disease and age, culminating into a score ranging from 0 (no nutritional risk) to 6 (high nutritional risk). In addition, concomitant disease, sociodemographic data, risk factors, and tumor data were recorded. The same data was collected for the historical control group using the hospital charting system. Following the intervention period, endpoint data was collected with the primary interest being overall wound complications within 30 days following surgery. Complications were categorized into wound dehiscence, abscess, fistula, hematoma, hemorrhage, seroma, or flap necrosis. Length of hospital stay was also recorded retrospectively, which included any readmissions. Finally, compliance with preoperative nutrition regimen was measured to form subgroups of compliance: 0-24%, 25-49%, 50-74%, and 75-100%. Compliance in the intervention group was impressive with 84.3% of the patients falling in the 75-100% compliance subgroup.

The data analysis showed a significantly lower rate of overall complications in the immunonutrition intervention group. This remained statistically significant after adjusting for demographics, risk factors, tumor typing, surgical procedure, flap, and comorbidities. It is also important to note there was a decreased rate of each subcategory of complications, but these were not statistically significant. There was also no significant difference found in the severity of complications. Lastly, the secondary outcome of length of stay was significantly decreased in the intervention group, with immunonutrition subjects staying in the hospital for a median of six days versus 17 days in the control group. Rates of readmission were not found to be significantly different between the groups.

A strength of this study was the compliance rate of the immunonutrition group, with 84.3% of the group taking 75% or more of the prescribed Impact. Despite this strong compliance, the authors note that the subgroups of the sample were too small to accurately note correlation between compliance and outcomes. Another strength was the significance of the primary outcome findings. The immunonutrition group had a significantly lower rate of complication at 35% when compared to the control group at 58% complication rate. Having found statistical significance, these findings are convincing and promising for future research. On the other hand, some important weaknesses were noted by the authors, mostly revolving around the retrospective nature of the study. Due to this design, there was no randomization and no blinding for the intervention group. Also, the sample size that was limited. One important acknowledgment by the authors was that the diagnosis related groups system in Switzerland (SwissDRG) was implemented in 2012 (between the historical patients and the intervention group) and aimed to expedite the discharge process. Based on these strengths and limitations, the authors appropriately concluded that preoperative immunonutrition was associated with a reduction in overall complication rate and consequent length of stay in patients undergoing salvage surgery for HNSCC after intitial radiation. Mueller et al. (2019) suggest that this high-risk population may benefit from immunonutrition due to its potential to improve tissue regeneration and immune response. Clinically, prospective randomized trials will be necessary to support the results of this study and suggest implementation in practice.

Vidal-Casariego et al. (2014) – Quality Rating: Positive

The purpose of the systemic review and meta-analysis by Vidal-Casariego et al. (2014) was to assess whether arginine-enriched enteral nutrition has an impact on complications and length of stay for head and neck cancer patients undergoing surgical intervention. A total of 62

studies were identified in the literature, but only six were included in this review, none of which were included in this evidence analysis project. The six included articles totaled 397 patients. Criteria for inclusion included: randomized dobule blinded control studies, English or Spanish, samples comprised of surgical human head and neck patients, and outcomes investigating complications of surgery and length of stay. The 56 other studies were excluded on the basis of being non-randomized, comparing two formulas with immunonutrition, and/or immunonutrition intervention without arginine. Therefore, all studies investigated arginine-based immunonutrition compared to isocaloric and isonitrogenous enteral formulas. The arginine-based immunonutrition intervention was implemented in the pre- and perioperative phase, the perioperative phase, or the post-operative phase. Postoperative outcomes were assessed, including fistula occurrence, surgical site infections, or other generalized infections. Additionally, length of stay was included in several of the studies as a secondary outcome. The arginine-based immunonutrition interventions were associated with significant reductions in fistulas and length of stay, which the authors suggest is interrelated. It is important to note that these results were found in each of the studies, regardless of timing of the arginine supplementation (perioperatively versus postoperatively). There was no statistically significant difference with immunonutrition implementation when looking at wound infections or other generalized infections.

This systemic review with meta-analysis had several strengths that add validity to the findings. The review followed PRISMA methodolgy and had no heterogeneity or publication bias noted. Additionally, the review focused on studies that assessed clinical outcomes in an effort to make a tangible difference in the care of this high-risk population. Specifically, the review is one of few that assessed optimal timing of immunonutrition for these patients to receive the most benefit. On the other hand, there were a few weaknesses noted of the design of

this review. There were a small number of high-quality studies included, especially after considering inclusion and exclusion criteria. Poor blinding and randomization was noted in several of the study designs. Lastly, several studies were included that were small in sample size. Therefore, the findings are more difficult to apply to the general population without further research on a larger scale. With limited quality studies available, Vidal-Casariego et al. (2014) appropriately concluded that arginine supplementation may reduce fistula occurrence and length of stay in the head and neck cancer surgical population. However, more high-quality research in this field is essential to strengthing this correlation. The authors also suggest further research in the cost-effectiveness of this intervention as it relates to the findings of these high quality studies.

Conclusion Statement – Grade: III (Limited)

Immunonutrition in the perioperative phase potentially improves post-surgical outcomes and reduces length of stay in head and neck cancer patients undergoing surgical intervention. Out of the six studies and one review included in this evidence analysis project, one focused on glutamine supplementation, four on arginine, one on omega-3 fatty acids, and the final study assessed combinations of arginine and omega-3 fatty acids. All but two studies found statistically significant postoperative benefits of immunonutrition. One of the two that did not have significant findings was limited by compliance of participants, but when assessing the compliant participants alone, statistical significance was noted. Five of the seven articles reviewed received a neutral rating, while the systemic review and one study received positive ratings.

Four of the seven articles analyzed had postoperative complications (wound or infection related) and length of stay as the key outcomes of interest. Of these articles, two had a neutral rating and two had a positive rating. All four articles found significant results, although one articles significance diminished after adjusting for demographic and tumor characteristics. One

of the studies found that preoperative immunonutrition was associated with a reduced rate of overall postoperative complications at a rate of 35% when compared with the control group rate of 58%. This same study also found that length of stay was significantly reduced to six days in the intervention group compared with 17 days in the control group. In the systemic review and meta-analysis, fistula occurrence was significantly decreased in immunonutrition intervention groups with a rate of 0-5.2% across studies, compared to the control group rates of 2.1-20.8% across studies. Additionally, this review found a reduced length of stay with immunonutrition interventions across all six studies reviewed. In another study, significant results were found when assessing the compliant portion of study participants. When adjusting for this compliance, the mean length of stay was reduced to 18 days compared to the control group at 25 days. Additionally, postoperative infectious complications were significantly reduced among the compliant subjects as well.

Two articles investigated albumin and anthropometric data as the main outcomes. Both of these studies had neutral ratings, but one was specific to glutamine-based immunonutrition and the other to arginine-based immunonutrition. One study found significant increase in serum albumin with arginine-based immunonutrition, but no significant difference in anthropometrics, including weight and fat free mass. The other study focused on glutamine-based immunonutrition and found significant differences in serum albumin and fat free mass between the intervention and control groups.

Unfortunately, current literature on this topic has historically been limited by small sample sizes and low compliance rates. Therefore, the clinical impact and generalizability of many studies has been limited as well. Despite several studies finding statistically significant

benefits of immunonutrition, it is difficult to implement these interventions into practice without stronger research findings to justify cost barriers.

Table 5.
Overview Table.

Author, Year, Study Design, Class, Rating	**Study Purpose**	**Study Population**	**Intervention**	**Outcomes**	**Strengths and Weaknesses**
Azman et al. (2015) Prospective Randomized Clinical Trial *Class: A* *Rating: Neutral*	The purpose was to evaluate the effects of glutamine supplementation in patients undergoing head and neck surgery in the aspects of nutritional status and quality of life scores.	N = 46 Inclusion: Head and neck cancer diagnosis; scheduled surgery to address primary tumor site or nodal disease; 20-75 years old Exclusion: Contraindication to enteral nutrition; severe liver or renal insufficiency; severe malnutrition; severe cancer cachexia or sarcopenia; inborn errors of metabolism; chemoradiotherapy or other concurrent treatment protocol	Glutamine Plus TID x 4 weeks following surgery	Serum albumin Fat-free mass Quality of life scores	<u>Strengths</u>: sample size is moderate for this population <u>Weaknesses</u>: non-blinded study design measurement tool for body composition

Author, Year, Study Design, Class, Rating	**Study Purpose**	**Study Population**	**Intervention**	**Outcomes**	**Strengths and Weaknesses**
Barajas-Galindo et al. (2019) Retrospective Observational *Class: B* *Rating: Neutral*	The purpose was to determine whether enteral immunonutrition (arginine-enriched formula) reduced length of stay and fistula occurrence in postoperative head and neck cancer patients.	N = 135 Inclusion: head and neck cancer diagnosis undergoing surgery; received nutrition support via NG enteral feedings; January 2012-August 2018 Exclusion: received enteral nutrition for less than four days; transferred to or from other services or hospitals; under the age of 18 years old; prior to January 2012 or after August 2018	Immunonutrition versus standard enteral formula	Fistula occurrence Length of stay Readmission rate 90-day mortality	<u>Strengths</u>: investigates *postoperative* nutrition intervention <u>Weaknesses</u>: retrospective nature control versus immunonutrition groups based on different timeframes in this hospital No monitoring of nutritional requirements

Author, Year, Study Design, Class, Rating	**Study Purpose**	**Study Population**	**Intervention**	**Outcomes**	**Strengths and Weaknesses**
Buijs et al. (2010) *Double-Blinded, Randomized Control Trial with Long-Term Follow-Up* *Class: A* *Rating: Neutral*	The purpose was to analyze the long-term effects (survival, recurrence, new cancer) of perioperative use of arginine supplementation in head and neck cancer patients that are deemed severely malnourished.	N = 56 (initial cohort) 32 (long-term survival study) Inclusion: undergoing surgery for head and neck cancer; severely malnourished (preoperative weight loss ≥10% over past 6 months); diagnosis of SCC oral cavity, larynx, oropharynx or hypopharynx Exclusion: receiving investigational drugs or steroids; renal insufficiency; hepatic failure; any genetic immune disorder; confirmed diagnosis of AIDS	Standard enteral nutrition versus arginine-enriched nutrition preoperatively and postoperatively via nasogastric tube	Long-term survival	<u>Strengths:</u> Long-term follow-up of cohort <u>Weaknesses</u>: Small sample size Confounding variables (such as lifestyle) were not accounted for in the design

Author, Year, Study Design, Class, Rating	**Study Purpose**	**Study Population**	**Intervention**	**Outcomes**	**Strengths and Weaknesses**
De Luis et al. (2013) Prospective Cohort *Class: B* *Rating: Neutral*	The purpose was to investigate effect of oral w3 enriched immunonutrition on nutritional and biochemical parameters in postoperative head and neck cancer patients.	N = 33 Inclusion: post-surgical ambulatory patient; oral or laryngeal cancer diagnosis Exclusion: impaired hepatic function; impaired renal function; ongoing infection; major gastrointestinal disease; autoimmune disorders; steroid treatment; active chemotherapy; medication that could modulate metabolism or weight	Two units of w3 enriched powdered formula per day for 12 weeks	Anthropometrics Lab values (albumin, prealbumin, transferrin)	<u>Strengths</u>: Long duration of intervention (95.9 days average) <u>Weaknesses</u>: Low overall sample size of 33 patients Limitations of study not addressed by authors

Author, Year, Study Design, Class, Rating	**Study Purpose**	**Study Population**	**Intervention**	**Outcomes**	**Strengths and Weaknesses**
Falewee et al. (2013) *Prospective Randomized, Double-Blinded Study* *Class: A* *Rating: Positive*	The purpose was to investigate whether immunonutrition could reduce general and surgical infectious complications and length of stay, and to assess the benefit of preoperative versus perioperative feedings.	N = 205 Inclusion: SCC oral, oropharynx, larynx or hypopharynx; anticipated surgery; postoperative enteral feedings for a minimum of 7 days; 18-75 years old; adequate hematopoietic, hepatic, and renal functions Exclusion: treated with neoadjuvant chemotherapy; radiation therapy to region within the past year; intake of oral supplements with immune nutrients; HIV positive; pregnant or breastfeeding women	Group A: 1000 kcal/day standard diet preoperatively, followed by 1500 kcal/day standard diet postoperatively Group B: 1000 kcal/day Impact immunonutrition pre-operatively, followed by 1500 kcal/day of standard diet postoperatively Group C: 1000 kcal/day Impact preoperatively, followed by 1500 kcal/day Impact post-operatively *Preoperative nutrition x 8 days, postoperative nutrition x 7-15 days	Incidence of infection (systemic, surgical site, or nosocomial pneumopathy) Length of stay	<u>Strengths</u>: Multicenter with large sample size Homogenous groups <u>Weaknesses</u>: Lack of compliance reduced the ability to analyze the large sample

Author, Year, Study Design, Class, Rating	**Study Purpose**	**Study Population**	**Intervention**	**Outcomes**	**Strengths and Weaknesses**
Mueller et al. (2019) *Single-Armed Study with Historical Cohort* *Class: C* *Rating: Neutral*	The purpose was to investigate if preoperative administration of immunonutrition would decrease complications in the high-risk population of head and neck cancer patients undergoing salvage surgery.	N = 96 Inclusion: undergoing salvage surgery; persistent, recurrent, or second primary HNSCC after curatively intended RT, CRT, RT with concomitant immunotherapy; tumor location in oral cavity, oropharynx, hypopharynx, larynx, or unknown primary in neck Exclusion: (C)RT that did not affect the operative field of salvage surgery with more than 50 Gray; treatment between January and June of 2012 due to lack of monitoring	Standard nutrition versus Immunonutrition drinks TID for 5 days before surgery	Overall wound complications within 30 days after surgery Length of stay	<u>Strengths</u>: Significance in results, specifically lower complication rate <u>Weaknesses</u>: No randomization or blinding Retrospective, historical control group Limited sample size

Author, Year, Study Design, Class, Rating	**Study Purpose**	**Study Population**	**Intervention**	**Outcomes**	**Strengths and Weaknesses**
Vidal-Casariego et al. (2014) Systemic Review with Meta-Analysis *Class: M* *Rating: Positive*	The purpose was to assess whether arginine-enriched enteral nutrition has an impact on complications and length of stay for head and neck cancer surgery patients.	N = 62 studies identified; 6 included Inclusion: Type of study (randomized, double blinded, controlled studies); English or Spanish; Samples of patients with head and neck cancer treated with surgery; Human studies; Outcomes investigating complications of surgery, length of stay; Jadad scale Exclusion: Non-randomized studies; Comparing two formulas with immunonutrition; Immunonutrition without arginine	Arginine-based immunonutrition compared to isocaloric and isonitrogenous enteral formula; Immunonutrition was implemented in Pre/Peri, Peri, or Post-operative phases	Postoperative outcomes (fistulas, surgical site infections, other infections) Length of stay	<u>Strengths</u>: Followed PRISMA methodology Focused on studies that assessed clinical outcomes Assessed optimal timing of immunonutrition No heterogeneity or publication bias <u>Weaknesses</u>: Small number of high-quality studies Poor blinding and randomization noted Small studies included

Chapter 5: Discussion

Evidence Summary

Head and neck cancer patients are at high nutritional risk due to locations of tumor burden and treatment impact. Enteral nutrition is often implemented for these same reasons, especially with surgical intervention. The optimal regimen and timing of enteral nutrition in this population is still under investigation. This evidence analysis project aimed to investigate the impact that immunonutrition implementation in the preoperative, perioperative and postoperative phases may have on the outcomes of patients undergoing head and neck cancer surgeries.

In total, seven studies were incorporated in this analysis that met the inclusion criteria for the project. Each article or review assessed immunonutrition in the form of arginine, glutamine, and/or w3 fatty acids. In total, four articles investigated arginine alone, including Barajas-Galindo et al. (2019), Buijs et al. (2010), Falewee et al. (2013) and Vidal-Casariego et al. (2014). Azman et al. (2015) investigated glutamine alone and De Luis et al. (2013) investigated w3 fatty acids alone. Lastly, Mueller et al. (2019) studied a combination of arginine and w3 fatty acids together. All studies were conducted on adult patients and occurred in the past 20 years. Article design varied greatly, with most articles being prospective randomized control trials or retrospective with historical cohorts. There was also one systemic review with meta-analysis included. The greatest variation between studies was the timing of the immunonutrition intervention. Mueller et al. (2019) focused on preoperative intervention. Buijs et al. (2010) and Falewee et al. (2013) focused on perioperative intervention. Lastly, Azman et al. (2015), Barajas-Galindo et al. (2019), and De Luis et al. (2013) focused on postoperative intervention with immunonutrition. The review by Vidal-Casariego et al. (2014) included many studies, all of which were either perioperative or postoperative interventions. Finally, in comparing quality of

the studies, five were deemed to have a neutral quality rating, while two were deemed to have a positive rating based on the Quality Criteria Checklist.

As discussed in chapter four, the findings of each article varied due to different outcomes of interest, but overall a correlation was found between immunonutrition in the perioperative or postoperative phase and improvement in post-surgical outcomes and length of stay. Some statistical significance shifted when the researchers adjusted for compliance, as this was a large barrier in this population such as with Falewee et al. (2013). These positive correlations were noted across immunonutrients, although most research being reviewed included arginine.

Limitation of Current Literature

This evidence analysis project revealed several limitations in the current literature. The primary limitation is the sheer quantity of studies available that investigate immunonutrition in the adult head and neck cancer surgery population. Even though this population is at great nutritional risk, the research has not been prevalent in immunonutrition interventions. In addition to the number of studies available in current research, another limitation of the is that the studies that have been conducted are often limited in subject sample size. This was partially attributed to cancer mortality; However, it was also noted in a few studies that compliance with the nutrition protocol was lacking and therefore the findings were limited by the resulting reduced sample size. Lastly, another limitation is that most studies included arginine as a component of the immunonutrition regimen. It has yet to be determined whether arginine is essential in showing benefits of immunonutrition, or if any immunonutrient will produce the same results. Each of these limitations in the current literature will need to be addressed by future research in order to appropriately apply findings to practice.

Applications for Future Practice

This EAL project brought together the available research on immunonutrition interventions in the high malnutrition risk head and neck cancer surgical patient population. The project's purpose was to determine if immunonutrition in the preoperative, perioperative or postoperative phases of head and neck cancer surgery could benefit outcomes such as length of stay and postoperative complications. Although there were limited studies available that met the inclusion criteria, analysis of the present literature is important in order to continue improving nutrition practice. This EAL project could impact clinical practice, as preliminary results suggest benefit from immunonutrition. Although the current literature may not be enough support to justify the cost of immunonutrition formulas for medical centers, it certainly is promising in supporting further investigation. With further correlation of positive outcomes, medical centers could prevent postoperative complications, reduce hospital stays, and therefore reduce overall cost associated with this high-risk population.

As discussed, present research showed promising outcomes with immunonutrition, specifically with postoperative implementation. Future research is necessary not only to contribute to the quantity of evidence available, but also to improve the quality of study designs on this topic. To better serve this population, future research will need to include greater recruitment of participants, more prospective randomized controlled trials and better regulation over compliance. If these components can be corrected in future research, findings will be more applicable to the general population and would become more likely to meet daily practice. If findings favor immunonutrition as this preliminary research has, it would provide stronger support for the cost-benefit analysis of implementation.

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Appendix I. Evidence Abstract Worksheet.

Citation	Azman, M., Mohd Yunus, M. R., Sulaiman, S., & Syed Omar, S. N. (2015). Enteral glutamine supplementation in surgical patients with head and neck malignancy: A randomized controlled trial. *Head & Neck, 37*(12), 1799–1807. https://doi.org/10.1002/hed.23839
Study Design	Randomized controlled trial
Class	A
Quality Rating	☐ + (Positive) ☐ - (Negative) ☒ ⊘ (Neutral)
Research Purpose	To evaluate the effects of glutamine supplementation in patients undergoing head and neck surgery in the aspects of nutritional status and quality of life scores.
Inclusion Criteria	• Diagnosed with head and neck cancer • Scheduled for surgery to address primary tumor site or nodal disease • 20-75 years old
Exclusion Criteria	• Contraindication to enteral nutrition • Severe liver or renal insufficiency (with lab determinants) • Severe malnutrition not amendable to enteral nutritional optimization • Severe cancer cachexia or sarcopenia • Patients with inborn errors of metabolism of nutrients contained in Glutamine Plus • Patients with head and neck malignancy going for chemoradiotherapy, including patients irradiated while on glutamine supplementation • Patients with head and neck cancer who had any form of concurrent treatment protocols during the study

Description of Study Protocol	Recruitment: January 2011 – June 2012 (18 months) Design: Included participants were randomized into interventional and control groups. No blinding was used. Data points (outlined below) were collected at baseline preoperatively. Glutamine Plus supplementation was provided to patients in the intervention group to take three times per day for four weeks postoperatively. The control group had no supplementation. Data points were again collected at 4-weeks post-operatively. Blinding used (if applicable): N/A Intervention (if applicable): Glutamine Plus TID x four weeks following surgery Statistical Analysis: Pearson chi-square test (analysis of demographic characteristics); t test (outcome differences between control and intervention group); Spearman correlation (to detect correlation between nutrition status and quality of life scores). Significance noted by $p < 0.05$.
Data Collection Summary	Timing of Measurements: At first visit before surgery, demographic data, fat-free mass measurement using BIA, quality of life score, serum albumin, and daily caloric intake assessed. At end of 4-week post-operative period, assessed 24-hour recall, quality of life scores, serum albumin, and body composition. Dependent Variables: quality of life scores, serum albumin, and body composition (fat-free mass) Independent Variables: Glutamine supplementation versus no intervention Control Variables: Surgical intervention

Description of Actual Data Sample	Initial: 46 Attrition (final N): 44 (24 Males 20 Females) Age: • 27.3% young adult • 54.6% middle adult • 18.2% elderly Ethnicity: • 59.1% Malay • 31.8% Chinese • 9.1% Indian Other relevant demographics: • 18.2% early stage cancer (I and II), 81.8% late stage cancer (III and IV) • Cancer location: o Oral cavity (38.6%) o Oropharynx (9.1%) o Nasopharynx (4.6%) o Paranasal sinuses (9.1%) o Larynx (25%) o Thyroid (2.3%) o Neck (4.6%) o Salivary gland (4.6%) Location: Universiti Kebangsaan Malaysia Medical Centre
Summary of Results	Key Findings: • Significant differences between control and intervention groups in regard to: o serum albumin ($p < 0.001$) o fat-free mass ($p < 0.001$) o quality of life scores ($p < 0.05$)

	• Significant correlation between fat-free mass and quality of life score ($p < 0.05$). Other Findings: • Effects of glutamine supplementation were found despite poor caloric intake and hypoalbuminemia in the intervention group prior to surgery.
Author Conclusion	Enteral glutamine supplementation significantly improves fat-free mass, serum albumin, and quality of life scores postoperatively and maintenance of lean body mass correlated with improved postoperative outcomes in terms of the patient's quality of life.
Reviewer Comments	• *Study strengths: sample size is moderate for this population* • *Study Limitations: non-blinded study design; measurement tool for body composition* *Overall, one study that suggests benefits of glutamine supplementation but further research is needed to change practice guidelines. Improvements can be made to future studies to reduce limitations.*
Funding Source	Grant: Universiti Kebangsaan Malaysia Fundamental Grant

Symbols Used	*Explanation*
+	*Positive – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	*Negative – Indicates that these issues have not been adequately addressed.*
⃠	*Neutral – indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
3. Were <u>study groups comparable</u>?	3	Yes

3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
3.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	N/A
3.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A

4. Was method of handling <u>withdrawals</u> described?	4	Yes
4.1. We**r**e follow up methods described and the same for all groups?	4.1	Yes
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4. Were reasons for withdrawals similar across groups	4.4	Yes
	4.5	N/A

4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?		
5. Was <u>blinding</u> used to prevent introduction of bias?	5	No
5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
	5.3	N/A
	5.4	N/A
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.5	N/A
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?		
5.5. In diagnostic study, were test results blinded to patient history and other test results?		
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Unclear
	6.1	Yes
	6.2	N/A
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.3	Yes
	6.4	Unclear
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.5	Yes
	6.6	N/A
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.7	Unclear
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.8	N/A
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?		
6.6. Were extra or unplanned treatments described?		
6.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?		

6.8. In diagnostic study, were details of test administration and replication sufficient?		
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
	7.1	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.2	Yes
	7.3	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.4	Yes
	7.5	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.6	Yes
7.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.7	Yes
7.5. Was the measurement of effect at an appropriate level of precision?		
7.6. Were other factors accounted for (measured) that could affect outcomes?		
7.7. Were the measurements conducted consistently across groups?		

8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Unclear
	8.1	Yes
8.1. Were statistical analyses adequately described the results reported appropriately?	8.2	Yes
	8.3	Yes
8.2. Were correct statistical tests used and assumptions of test not violated?	8.4	Unclear
	8.5	Yes
8.3. Were statistics reported with levels of significance and/or confidence intervals?	8.6	Yes
8.4. Was “intent to treat” analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.7	N/A

8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? 8.6. Was clinical significance as well as statistical significance reported? 8.7. If negative findings, was a power calculation reported to address type 2 error?		
9. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?** 9.1. Is there a discussion of findings? 9.2. Are biases and study limitations identified and discussed?	9 9.1 9.2	Yes Yes Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely? 10.1. Were sources of funding and investigators' affiliations described? 10.2. Was there no apparent conflict of interest?	10 10.1 10.2	Yes Yes Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Citation	Barajas-Galindo, D. E., Vidal-Casariego, A., Pintor-de la Maza, B., Fernandez-Martinez, P., Ramos-Martinez, T., Garcia-Arias, S., Hernandez-Moreno, A., Urioste-Fondo, A., Cano-Rodriguez, I., Ballesteros-Pomar, M. D. (2019). Postoperative enteral immunonutrition in head and neck cancer patients: Impact on clinical outcomes. *Endocrinologia, Diabetes y Nutricion, 67*(1), 13-19. doi:10.1016/j.endinu.2019.05.006
Study Design	Retrospective observational
Class	B
Quality Rating	☐ + (Positive) ☐ - (Negative) ☒ ⊘ (Neutral)
Research Purpose	To determine whether enteral immunonutrition (arginine-enriched formula) reduced length of stay and fistula occurrence in postoperative head and neck cancer patients
Inclusion Criteria	• Undergoing surgery • Head and neck cancer patients • Received nutrition support via nasogastric enteral feedings • Between January 2012 and August 2018
Exclusion Criteria	• Less than 4 days of enteral nutrition • Patients transferred to or from other services or from another hospital • Patients under 18 years old • Prior to January 2012 or after August 2018
Description of Study Protocol	Recruitment: 135 patients Design: Any patient admitted from January 2012 to August 2018 who received nasogastric enteral nutrition was retrospectively reviewed. Patients that received immunonutrition (IMPACT) were compared to the control group (patients on standard formula enteral feedings).

	Statistical Analysis: Chi-squared test to compare qualitative variables; Student's t-test or Mann-Whitney U test for variables of 2 categories; ANOVA or Kruskal-Wallis for variables of more than 2 categories; Pearson or Spearman correlation tests for quantitative variables. Level of significance for all: 5%.
Data Collection Summary	Timing of Measurements: Sociodemographic, anthropometric, and nutritional intervention were recorded after surgery. Fasting blood samples of albumin and retinol-binding protein were collected weekly. Fistula appearance, LoS, readmissions, and 90-day mortality were recorded as well. Dependent Variables: Clinical outcomes (fistula occurrence, length of stay, readmission rate, and 90-day mortality) Independent Variables: type of feeding (immunonutrition versus standard enteral formula) Control Variables: Surgical intervention
Description of Actual Data Sample	Initial: 135 (119 Males 16 Females) Attrition (final N): 135 Study Groups: Standard formula (n=67); Immunonutrition (n=68) Age (mean): 66.99 years (standard formula), 65.58 years (immunonutrition formula), 66.28 years (overall average) Other relevant demographics: No statistically significant differences found between groups • Cancer Type o Larynx (69.63%) o Oropharynx (7.41%) o Nasopharynx (6.67%)

	○ Oral Cavity (14.07%) ○ Thyroid (2.22%) • Tumor Staging ○ I (7.34%) ○ II (14.68%) ○ III (27.52%) ○ IVA (42.20%) ○ IVB (2.75%) ○ IVC (5.50%) • Nutritional Status (ICD-10) ○ E40 (8.89%) ○ E41 (47.41%) ○ E43 (14.07%) ○ E44.0 (8.15%) ○ E44.1 (9.63%) ○ R13.1 (11.85%) Anthropometrics: • No statistically significant differences in weight or albumin levels; statistically insignificant elevation in RBP in the immunonutrition group at the end of hospitalization Location: Clinical Nutrition and Dietetic Unit, Department of Endocrinology and Nutrition, Complejo Asistencial Universitario de León, León, Spain
Summary of Results	Key Findings: • Fistula appearance was significantly higher in the standard nutrition group (p=0.047) • After adjusting for age, tumor stage, aggressiveness of surgery, energy intake and preoperative malnutrition status, preoperative malnutrition status was significantly associated with higher incidence of fistula (p=0.041)

	• Length of stay was significantly longer in the standard group (p=0.030) • After adjusting for age, tumor stage, enteral formula, aggressiveness of surgery and preoperative malnutrition, the presence of a fistula was associated with an increased risk of readmission during the three-month period following discharge (p < 0.001) Other Findings: • Patients with fistula had a significantly increased length of stay (p < 0.001) • No significant difference in 90-day mortality rate between formulas nor based on fistula occurrence
Author Conclusion	Arginine-enriched immunonutrition formula for enteral nutrition may reduce risk of fistula development and length of hospital stay.
Reviewer Comments	• *Study strengths: new evidence supporting nutrition intervention prior to surgery* • *Study Limitations: retrospective nature, control versus immunonutrition groups based on different timeframes in this hospital* *Exhibited link between preoperative nutrition status and postoperative complication (fistula), suggesting need for early nutrition intervention in surgical candidates*
Funding Source	Self-funded

Symbols Used	*Explanation*
+	*Positive – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*

--	*Negative – Indicates that these issues have not been adequately addressed.*
⊘	*Neutral – indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions		
5. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
6. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
7. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
8. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
11. Was the <u>research question</u> clearly stated?	1	Yes
11.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
	1.2	Yes
11.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.3	Yes
11.3. Were the target population and setting specified?		
12. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
12.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis	2.1	Yes
	2.2	Yes
	2.3	Yes

criteria), and with sufficient detail and without omitting criteria critical to the study? 12.2. Were criteria applied equally to all study groups? 12.3. Were health, demographics, and other characteristics of subjects described? 12.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
13. Were <u>study groups comparable</u>? 13.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) 13.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? 13.3. Were concurrent controls used? (Concurrent preferred over historical controls.) 13.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? 13.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) 13.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3	Unclear
	3.1	N/A
	3.2	Yes
	3.3	No
	3.4	Yes
	3.5	N/A
	3.6	N/A

14. Was method of handling <u>withdrawals</u> described?	4	Yes
	4.1	N/A

14.1. Were follow up methods described and the same for all groups?	4.2	N/A
	4.3	Yes
14.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.4	N/A
14.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.5	N/A
14.4. Were reasons for withdrawals similar across groups		
14.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?		
15. Was <u>blinding</u> used to prevent introduction of bias?	5	N/A
15.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	N/A
	5.2	N/A
15.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.3	N/A
	5.4	N/A
15.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.5	N/A
15.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?		
15.5. In diagnostic study, were test results blinded to patient history and other test results?		
16. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Unclear
	6.1	N/A
	6.2	Yes
16.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.3	N/A
	6.4	Unclear
16.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.5	N/A
	6.6	N/A

16.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? 16.4. Was the amount of exposure and, if relevant, subject/patient compliance measured? 16.5. Were co-interventions (e.g., ancillary treatments, other therapies) described? 16.6. Were extra or unplanned treatments described? 16.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? 16.8. In diagnostic study, were details of test administration and replication sufficient?	6.7 6.8	N/A N/A
17. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>? 17.1. Were primary and secondary endpoints described and relevant to the question? 17.2. Were nutrition measures appropriate to question and outcomes of concern? 17.3. Was the period of follow-up long enough for important outcome(s) to occur? 17.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? 17.5. Was the measurement of effect at an appropriate level of precision? 17.6. Were other factors accounted for (measured) that could affect outcomes? 17.7. Were the measurements conducted consistently across groups?	7 7.1 7.2 7.3 7.4 7.5 7.6 7.7	Yes Yes Yes Yes Yes Yes Yes Yes

18. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8 8.1	Yes Yes

18.1. Were statistical analyses adequately described the results reported appropriately?	8.2	Yes
	8.3	Yes
18.2. Were correct statistical tests used and assumptions of test not violated?	8.4	N/A
	8.5	Yes
18.3. Were statistics reported with levels of significance and/or confidence intervals?	8.6	Yes
18.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? 18.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? 18.6. Was clinical significance as well as statistical significance reported? 18.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
19. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
	9.1	Yes
19.1. Is there a discussion of findings? 19.2. Are biases and study limitations identified and discussed?	9.2	Yes
20. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
20.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
20.2. Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅)		

If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*

Citation	Buijs, N., Van Bokhorst-de van der Schueren, M. A., Langius, J., Leemans, C. R., Kuik, D. J., Vermeulen, M., & Van Leeuwen, P. (2010). Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival. *American Journal of Clinical Nutrition,* 92, 1151-1156. doi:10.3945/ajcn.2010.29532
Study Design	Double-blind, randomized, controlled with long-term follow-up
Class	A
Quality Rating	☐ + (Positive) ☐ - (Negative) ☒ ⊘ (Neutral)
Research Purpose	To analyze the long-term effects (survival, recurrence, new cancer) of perioperative use of arginine supplementation in head and neck cancer patients that are deemed severely malnourished.
Inclusion Criteria	• Undergoing head and neck cancer surgery • Severely malnourished (preoperative weight loss ≥10% over past 6 months) • Diagnosis of squamous cell carcinoma of oral cavity, larynx, oropharynx, or hypopharynx
Exclusion Criteria	• Receiving investigational drugs or steroids • Renal insufficiency • Hepatic failure • Any genetic immune disorder • Confirmed diagnosis of AIDS
Description of Study Protocol	Recruitment: 56 patients in initial cohort 32 patients in long-term survival study Design: Between 1994-1997, the original double blinded study assessed 56 patients undergoing head and neck cancer surgery that were severely malnourished. Patients were randomly assigned to arginine-supplemented enteral formula or standard enteral formula for preoperative (7-10 days prior to surgery) and postoperative enteral nutrition. Oral intake permitted

	per results of imaging 10 days post-op. The present study assesses the 10-year survival of participants through data collection on survival/death, recurrence, occurrence of metastases, and occurrence of second primary tumors. The cause of death was noted. Blinding used (if applicable): Double-blind (both products blinded, independent statistician generated blinding procedure) Intervention (if applicable): Standard enteral nutrition (control) vs arginine-enriched nutrition (intervention group) preoperatively and postoperatively via nasogastric tube. Statistical Analysis: Log-rank tests (comparing survival between groups), Cox regression (confounding and effect modification. Level of significance measured by p-value < 0.05.
Data Collection Summary	Timing of Measurements: August 2007 (≥ 10 years from original data collection, surgeries) Dependent Variables: Long-term survival Independent Variables: Type of nutrition (arginine-supplemented or standard enteral nutrition)

Description of Actual Data Sample	Initial: 32 (19 Males 13 Females)
	Attrition (final N): 32
	Age (mean): 59 in arginine group, 60 in control group
	Other relevant demographics:
	• Tumor Stage
	  ○ III (15.63%)
	  ○ IVa (50%)
	  ○ IVb (0%)
	  ○ Recurrent tumor (31.25%)

	○ Not staged (3.13%) • Tumor Location ○ Oral Cavity (9.38%) ○ Larynx (18.75%) ○ Oropharynx (40.63%) ○ Hypopharynx (25.0%) ○ Other (6.25%) Anthropometrics: • No significant difference in age, sex, tumor stage, tumor location, comorbidity, weight loss, type of operation, or type of reconstructive surgery Location: VU University Medical Center, MB Amsterdam, Netherlands
Summary of Results	Key Findings: • 29 of the 32 participants had died by the 10-year survival study: all 15 patients in the control group and 14 of 17 in the intervention group had died. • The median overall long-term survival was 34.8 months in the intervention group and 20.7 months in the control group (p=0.019) • Disease-specific survival was 94.4 months in the intervention group and 20.8 months in the control group (p=0.022) • When accounting for confounders, difference in survival remained significant (p=0.031) Other Findings: • Locoregional recurrence could be *estimated* at 92.8 months for intervention group versus 10.6 months for the control group (p=0.027) • No statistically significant difference in distant metastases or second primary diseases
Author Conclusion	The findings suggest perioperative arginine-enriched nutrition may improve long-term survival in malnourished head and neck cancer

	surgical candidates. Larger sampling is needed to strengthen these findings.
Reviewer Comments	• *Study strengths: Long-term follow up* • *Study weaknesses: small sample size, confounding variables (such as lifestyle) were not accounted for in this design* • *Suggests improved longevity with perioperative immunonutrition implementation, however, further research with larger sample sizes is needed to support findings of this small study.*
Funding Source	Nutricia Nederland BV (did not participate in process)

Symbols Used	*Explanation*
+	*Positive – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	*Negative – Indicates that these issues have not been adequately addressed.*
⊘	*Neutral – indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes

If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
	2.2	Yes
	2.3	Yes
2.2. Were criteria applied equally to all study groups?	2.4	Yes
2.3. Were health, demographics, and other characteristics of subjects described?		
2.4. Were the subjects/patients a representative sample of the relevant population?		
3. Were <u>study groups comparable</u>?	3	Unclear
3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
	3.2	Yes
3.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.3	Yes
	3.4	Unclear
3.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.5	N/A
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were	3.6	N/A

preexisting differences accounted for by using appropriate adjustments in statistical analysis? 3.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) 3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?		

4. Was method of handling <u>withdrawals</u> described?	4	Yes
4.1. We**r**e follow up methods described and the same for all groups?	4.1	N/A
	4.2	N/A
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.3	Yes
	4.4	N/A
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.5	N/A
4.4. Were reasons for withdrawals similar across groups		
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?		
5. Was <u>blinding</u> used to prevent introduction of bias?	5	Yes
5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	Yes
	5.2	Yes
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.3	Yes
	5.4	N/A
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.5	N/A

5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status? 5.5. In diagnostic study, were test results blinded to patient history and other test results?		
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described? 6.1. In RCT or other intervention trial, were protocols described for all regimens studied? 6.2. In observational study, were interventions, study settings, and clinicians/provider described? 6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? 6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured? 6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described? 6.6. Were extra or unplanned treatments described? 6.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? 6.8. In diagnostic study, were details of test administration and replication sufficient?	6 6.1 6.2 6.3 6.4 6.5 6.6 6.7 6.8	Yes Yes N/A Yes Yes N/A N/A Yes N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>? 7.1. Were primary and secondary endpoints described and relevant to the question? 7.2. Were nutrition measures appropriate to question and outcomes of concern? 7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7 7.1 7.2 7.3 7.4 7.5 7.6 7.7	Unclear Yes Yes Yes Yes Yes Unclear Yes

7.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? 7.5. Was the measurement of effect at an appropriate level of precision? 7.6. Were other factors accounted for (measured) that could affect outcomes? 7.7. Were the measurements conducted consistently across groups?		

8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators? 8.1. Were statistical analyses adequately described the results reported appropriately? 8.2. Were correct statistical tests used and assumptions of test not violated? 8.3. Were statistics reported with levels of significance and/or confidence intervals? 8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? 8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? 8.6. Was clinical significance as well as statistical significance reported? 8.7. If negative findings, was a power calculation reported to address type 2 error?	8 8.1 8.2 8.3 8.4 8.5 8.6 8.7	Unclear Yes Yes Yes N/A No Yes N/A
9. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?** 9.1. Is there a discussion of findings?	9 9.1 9.2	Yes Yes Yes

9.2. Are biases and study limitations identified and discussed?		
10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
10.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
10.2. Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)

If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (∅)

If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)

If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Citation	De Luis, D., Izaola, O., Cuellar, L., Terroba, M., Ventosa, M., Martin, T., & Aller, R. (2013). Clinical effects of a w3 enhanced powdered nutritional formula in postsurgical ambulatory head and neck cancer patients. *Nutricion Hospitalaria, 28*, 1463-1467. doi:10.3305/nh.2013.28.5.6662
Study Design	Prospective Cohort Study
Class	B
Quality Rating	☐ + (Positive) ☐ - (Negative) ☒ ⊘ (Neutral)
Research Purpose	To investigate effect of oral w3 enriched immunonutrition on nutritional and biochemical parameters in postoperative head and neck cancer patients.
Inclusion Criteria	• Post-surgical • Ambulatory • Oral or laryngeal cancer
Exclusion Criteria	• Severe/moderate impaired hepatic function (total bilirubin concentration > 3 mg/dl) • Severe/moderate impaired renal function (serum creatinine concentration > 2 mg/dl) • Ongoing infections • Major gastrointestinal disease • Autoimmune disorders • Steroids treatment • Active chemotherapy • Medication that could modulate metabolism or weight
Description of Study Protocol	Recruitment: 33 patients Design: Participants with oral or laryngeal cancer who were postoperative and ambulatory were asked to consume two units of w3 enriched powdered formula per day for 12 weeks.

	Blinding used (if applicable): None noted Intervention (if applicable): Two units of w3 enriched powdered formula per day for 12 weeks Statistical Analysis: Kolmogorov-Smirnov test (distribution of variables); two tailed paired Student s t-test (quantitative variables with normal distribution); Wilcoxon test (non-parametric variables). Statistical significance measured by $p < 0.05$.

Data Collection Summary	May 2011 to April 2013
	
	Timing of Measurements:
	• Baseline (hospital discharge) complete history and physical exam with general assessment of nutrition status (anthropometrics)
	• Three-day diet recalls at baseline and week 12
	  o Phone call from dietitian every 14 days
	  o Mean total energy and macronutrient intake recorded based on recalls
	• Lab parameters at baseline and 12 weeks (albumin, prealbumin, transferrin, lymphocytes)
	Dependent Variables: Anthropometrics and lab values
	
	Independent Variables: W3 supplementation

Description of Actual Data Sample	Initial: 33 (27 Males 6 Females)
	No radiotherapy group (n=18); Radiotherapy group (n=15)
	Attrition (final N): 33
	Age (mean): 61.3 years
	Other relevant demographics:
	• Disease Stage:
	  o I (n=0)
	  o II (n=0)

	○ III (n=12) ○ IV (n=16) • Diagnosis of disease: ○ Oral Cavity (n=8) ○ Larynx (n=20) Anthropometrics: • Body weight (mean): 67.8 ± 9.3 kg Location: Medicine School and Unit of Investigation Hospital Rio Hortega. University of Valladolid, Valladolid, Spain.
Summary of Results	Key Findings: • Significant improvement in albumin, prealbumin, and transferrin concentrations after 12 weeks of w3 supplementation ($p < 0.05$) • Significant improvement in weight for patients with supplementation but not on radiotherapy ($p < 0.05$) Other Findings: • Data suggests weight stability with net gain of lean body mass.
Author Conclusion	Omega-3 enhanced powdered nutritional formula improved blood protein concentrations in this population. Without radiotherapy, patients experienced improved weight, fat mass, and fat free mass.
Reviewer Comments	• *Study strengths: long duration of intervention (95.9 days average)* • *Study weaknesses: low overall sample size of 33* *Further research with larger sample size is needed to confirm statistical significance of benefits of w3 supplementation. Authors did not address limitations of study.*
Funding Source	None noted

Symbols Used	*Explanation*
+	*Positive – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*

--	*Negative – Indicates that these issues have not been adequately addressed.*
⊘	*Neutral – indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and	2.1	Yes
	2.2	Yes

with sufficient detail and without omitting criteria critical to the study? 2.2. Were criteria applied equally to all study groups? 2.3. Were health, demographics, and other characteristics of subjects described? 2.4. Were the subjects/patients a representative sample of the relevant population?	2.3	Yes
	2.4	Yes
3. Were <u>study groups comparable</u>? 3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) 3.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? 3.3. Were concurrent controls used? (Concurrent preferred over historical controls.) 3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? 3.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) 3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3	Yes
	3.1	N/A
	3.2	Yes
	3.3	N/A
	3.4	Yes
	3.5	N/A
	3.6	N/A

4. Was method of handling <u>withdrawals</u> described?	4	Yes
	4.1	Yes

4.1. Were follow up methods described and the same for all groups? 4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) 4.3. Were all enrolled subjects/patients (in the original sample) accounted for? 4.4. Were reasons for withdrawals similar across groups 4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.2 4.3 4.4 4.5	N/A Yes N/A N/A
5. Was <u>blinding</u> used to prevent introduction of bias? 5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? 5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) 5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? 5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status? 5.5. In diagnostic study, were test results blinded to patient history and other test results?	5 5.1 5.2 5.3 5.4 5.5	N/A N/A N/A N/A N/A N/A
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described? 6.1. In RCT or other intervention trial, were protocols described for all regimens studied? 6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6 6.1 6.2 6.3 6.4 6.5 6.6 6.7	Yes Yes Yes Yes Yes Yes N/A Yes

6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? 6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured? 6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described? 6.6. Were extra or unplanned treatments described? 6.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? 6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>? 7.1. Were primary and secondary endpoints described and relevant to the question? 7.2. Were nutrition measures appropriate to question and outcomes of concern? 7.3. Was the period of follow-up long enough for important outcome(s) to occur? 7.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? 7.5. Was the measurement of effect at an appropriate level of precision? 7.6. Were other factors accounted for (measured) that could affect outcomes? 7.7. Were the measurements conducted consistently across groups?	7 7.1 7.2 7.3 7.4 7.5 7.6 7.7	Unclear Yes Yes Yes Yes Yes Unclear Yes

8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8 8.1	Unclear Yes

8.1. Were statistical analyses adequately described the results reported appropriately? 8.2. Were correct statistical tests used and assumptions of test not violated? 8.3. Were statistics reported with levels of significance and/or confidence intervals? 8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? 8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? 8.6. Was clinical significance as well as statistical significance reported? 8.7. If negative findings, was a power calculation reported to address type 2 error?	8.2 8.3 8.4 8.5 8.6 8.7	Yes Unclear N/A N/A Yes N/A
9. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?** 9.1. Is there a discussion of findings? 9.2. Are biases and study limitations identified and discussed?	9 9.1 9.2	No Yes No
10. Is bias due to study's <u>funding or sponsorship</u> unlikely? 10.1. Were sources of funding and investigators' affiliations described? 10.2. Was there no apparent conflict of interest?	10 10.1 10.2	No No Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*		

PLUS/POSITIVE (+)

If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Citation	Falewee, M., Schilf, A., Boufflers, E., Cartier, C., Bachmann, P., Pressoir, M., Banal, A., Michel, C., Ettaiche, M. (2013). Reduced infections with perioperative immunonutrition in head and neck cancer: Exploratory results of a multicenter, prospective, randomized, double-blind study. *Clinical Nutrition, 33*, 776-784. doi:10.1016/j.clnu.2013.10.006
Study Design	Prospective, randomized, double-blind
Class	A
Quality Rating	☒ + (Positive) ☐ - (Negative) ☐ ⊘ (Neutral)
Research Purpose	To investigate whether immunonutrition could reduce general and surgical infectious complications and length of stay, and to assess the benefit of preoperative versus perioperative feedings.
Inclusion Criteria	• Confirmed squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx • Anticipated surgery • Postoperative enteral feeding for a minimum of seven days • 18-75 years old • Adequate hematopoietic function, hepatic function, and renal function
Exclusion Criteria	• Patients treated with neo-adjuvant chemotherapy • Radiation therapy to head and neck region during the previous year • Intake of oral nutrition supplements with immune nutrients before study entry • Patients testing positive for HIV

	• Pregnant or breast-feeding women
Description of Study Protocol	Recruitment: 312; Recruitment was conducted across 8 centers in France starting in July 2007. Design: Eligible patients were randomly allocated to one of three groups: • Group A (n=97) received 1000 kcal/day standard diet preoperatively, followed by 1500 kcal/day standard diet postoperatively. Overall, n=64 for total analyzed members of Group A. • Group B (n=102) received 1000 kcal/day Impact immunonutrition pre-operatively, followed by 1500 kcal/day of standard diet postoperatively. Overall, n=68 for total analyzed members of Group B. • Group C (n=99) received 1000 kcal/day Impact preoperatively, followed by 1500 kcal/day Impact post-operatively. Overall, n=73 for total analyzed members of Group C. Preoperative nutrition lasted for 8 days prior to surgery and postoperative nutrition was implemented for 7-15 days after surgery. Compliance was assessed. Blinding used (if applicable): Allocation of patients to groups was independently conducted by Pharmacy of Clinical Trials units; Double-blinding implemented with labels to minimize bias. Intervention (if applicable): Immunonutrition (Impact) preoperatively or perioperatively. See group outlines above. Statistical Analysis: X^2 test/Fisher test (qualitative data); Student t test/Wilcoxon test (quantitative data). Statistical significance measured by $p < 0.05$.
Data Collection Summary	Timing of Measurements: Patients were followed for 90 days following surgery to monitor for the primary outcome of infection (systemic,

	surgical site, or nosocomial pneumopathy). Compliance was monitored throughout. Dependent Variables: Incidence of infection (systemic, surgical site, or nosocomial pneumopathy) Independent Variables: Type of nutrition (standard, preoperative immunonutrition or perioperative immunonutrition)

Description of Actual Data Sample	Initial: 312
	Attrition (final N): 205 (172 Males 33 Females)
	Age (mean): 58.9 years
	Other relevant demographics:
	• Risk Factors – no statistical difference
	  o Alcohol and tobacco use
	  o COPD
	  o T2DM
	  o Vascular disease
	• Tumor location – no statistical difference
	  o Bucopharynx (152 participants)
	  o Pharyngolarynx (53 participants)
	• Tumor Stage – no statistical difference
	Anthropometrics:
	• Mean weight, height, BMI – no statistical difference between groups
	• Percent weight loss, dysphagia, nutritional status – no significant difference between groups
	Locations:
	1. Centre Antoine Lacassagne – Nice, France
	2. Institut Gustave Roussy – Villejuif, France
	3. Centre Oscar Lambret – Lille, France

	4. Centre Hospitalier Universitaire of Montpellier – Montpellier, France 5. Centre Léon Bérard – Lyon, France 6. Institut Claudius Reguad – Toulouse, France 7. Centre René Huguenin – Paris, France
Summary of Results	Key Findings: • Infection was found in 51.2% of all patients; 54.7% in Group A (control group), 54.4% in Group B (preoperative immunonutrition) and 45.2% in Group C (perioperative immunonutrition). This was **not** statistically significant with a p-value of 0.44. • Statistical significance was also not found for surgical site infections or mean length of stay (p=0.47 and p=0.626 accordingly). Other Findings: • When patients consumed 75% of prescribed calorie intake, there was a significant difference in surgical site infections between the control and perioperative immunonutrition groups (p=0.04). Length of stay was significantly increased if the patient developed a postoperative infectious complication ($p < 0.001$).
Author Conclusion	The Intent to Treat (ITT) population saw no significant difference in IC, SSI, and LOS. Further research is needed to investigate the positive results found regarding perioperative immunonutrition use with compliance of regimens.
Reviewer Comments	• *Study strengths: multicenter with large sample (n=312, n=205 analyzed), homogenous groups* • *Study weaknesses: lack of compliance reduced ability to analyze large sample* *Further research with better compliance to nutrition protocol is needed to discern any correlation between immunonutrition and infection risk, as well as preoperative versus perioperative benefit.*

Funding Source	Nestlé supplied Impact Supported by grants from the French National Cancer Institute

Symbols Used	*Explanation*
+	*Positive – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	*Negative – Indicates that these issues have not been adequately addressed.*
⊘	*Neutral – indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
	1.2	Yes
	1.3	Yes

1.2. Was the outcome(s) (dependent variable(s)) clearly indicated? 1.3. Were the target population and setting specified?		
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
	2.2	Yes
	2.3	Yes
2.2. Were criteria applied equally to all study groups? 2.3. Were health, demographics, and other characteristics of subjects described? 2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
3. Were <u>study groups comparable</u>?	3	Yes
3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
	3.2	Yes
3.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.3	Yes
	3.4	Yes
3.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.5	N/A
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? 3.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.6	N/A

3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?		
4. Was method of handling <u>withdrawals</u> described?	4	Yes
4.1. We**r**e follow up methods described and the same for all groups?	4.1	Yes
	4.2	Yes
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.3	Yes
	4.4	Yes
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.5	N/A
4.4. Were reasons for withdrawals similar across groups		
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?		
5. Was <u>blinding</u> used to prevent introduction of bias?	5	Yes
5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	Yes
	5.2	Yes
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.3	Yes
	5.4	N/A
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.5	N/A
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?		
5.5. In diagnostic study, were test results blinded to patient history and other test results?		
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
	6.1	Yes
	6.2	N/A
	6.3	Yes

6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.4	Yes
	6.5	N/A
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.6	N/A
	6.7	Yes
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? 6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured? 6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described? 6.6. Were extra or unplanned treatments described? 6.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? 6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
	7.1	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.2	Yes
	7.3	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.4	Yes
	7.5	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.6	Yes
7.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? 7.5. Was the measurement of effect at an appropriate level of precision? 7.6. Were other factors accounted for (measured) that could affect outcomes?	7.7	Yes

7.7. Were the measurements conducted consistently across groups?		
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators? 8.1. Were statistical analyses adequately described the results reported appropriately? 8.2. Were correct statistical tests used and assumptions of test not violated? 8.3. Were statistics reported with levels of significance and/or confidence intervals? 8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? 8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? 8.6. Was clinical significance as well as statistical significance reported? 8.7. If negative findings, was a power calculation reported to address type 2 error?	8 8.1 8.2 8.3 8.4 8.5 8.6 8.7	Unclear Yes Yes Yes Yes Unclear Yes Unclear
9. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?** 9.1. Is there a discussion of findings? 9.2. Are biases and study limitations identified and discussed?	9 9.1 9.2	Yes Yes Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely? 10.1. Were sources of funding and investigators' affiliations described? 10.2. Was there no apparent conflict of interest?	10 10.1 10.2	Unclear Yes Unclear
MINUS/NEGATIVE (-)		

If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*

Citation	Mueller, S. A., Mayer, C., Bojaxhiu, B., Aeberhard, C., Schuetz, P., Stanga, Z., & Giger, R. (2019). Effect of preoperative immunonutrition on complications after salvage surgery in head and neck cancer. *Journal of Otolaryngology - Head & Neck Surgry, 48*(25), 1-9. doi:10.1186/s40463-019-0345-8
Study Design	Single-armed with historical control
Class	C
Quality Rating	☐ + (Positive) ☐ - (Negative) ☒ ⊘ (Neutral)
Research Purpose	To investigate if preoperative administration of immunonutrition would decrease complications in the high-risk population of head and neck cancer patients undergoing salvage surgery.
Inclusion Criteria	• Undergoing salvage surgery • Persistent/recurrent or second primary HNSCC after curatively intended RT, CRT, RT with concomitant immunotherapy (Cetuximab)

	• Tumor location: oral cavity, oropharynx, hypopharynx, larynx, or carcinoma of unknown primary (CUP) of the neck
Exclusion Criteria	• If (C)RT did not affect the operative field of salvage surgery with more than 50 Gray • Patients treated between January-June 2012 due to lack of monitoring of compliance
Description of Study Protocol	Recruitment: Participants treated between July 2012 and September 2016 (intervention group) and between July 2008 and December 2011 (control group) Design: Subjects were scheduled for salvage surgery following radiotherapy treatment course. Patients in the intervention group received immunonutrition (Impact) x 3 units for 5 days prior to surgery. Primary outcome assessed was overall wound complications within the first 30 days after surgery. Intervention (if applicable): Immunonutrition drinks TID for 5 days before surgery. Statistical Analysis: Chi-square (Wald) test (frequency comparisons); Mann-Whitney U-test (two-group comparisons); univariate and multivariate regression analyses to determine effect of intervention and account for confounders.
Data Collection Summary	Timing of Measurements: Before implementation of immunonutrition, 30 days after surgery. Dependent Variables: Overall wound complications within 30 days after surgery; secondary: length of stay Independent Variables: Type of preoperative regimen (standard or immunonutrition)

	Control Variables: Radiotherapy

Description of Actual Data Sample	Initial: 96 (76 Males 20 Females)
	Attrition (final N): 96
	Age (mean): 65.4 years
	Other relevant demographics:
	• No significant difference in smoking or alcohol use
	• No significant difference in comorbidities
	• Cancer location:
	  ○ Oral Cavity (31%)
	  ○ Oropharynx (21%)
	  ○ Hypopharynx (9%)
	  ○ Larynx (26%)
	  ○ Lymph node recurrence (13%)
	• Stage of tumor
	  ○ I (22%)
	  ○ II (26%)
	  ○ III (22%)
	  ○ IV (30%)
	• No significant difference in surgery characteristics
	• Median of 524 days between RT to surgery
	Anthropometrics:
	• Average BMI of 23.29
	Location: Bern University Hospital, University of Bern – Bern, Switzerland

Summary of Results	Key Findings: • Significant reduction in patients suffering complications (35% in the intervention versus 58% in the control – p=0.049)

	• Significant reduction in length of stay for patients receiving the intervention (6 days) when compared to control group (17 days) (p=0.011) Other Findings: • Results believed to be attributed to immunonutrition's role in tissue regeneration and the immune response.
Author Conclusion	Favorable effects on complications and length of stay were found in this population when implementing preoperative immunonutrition.
Reviewer Comments	• *Study strengths: found significant results, specifically a lower complication rate* • *Study weaknesses: no randomization, blinding; retrospective, historical control group; limited number of patients* *Further research with larger sample sizes will be necessary to confirm these results.*
Funding Source	Research funds of Department of Diabetes, Endocrinology, Clinical Nutrition and Metabolism, and the Department of Oto-Rhino-Laryngology of University Hospital of Bern, Switzerland Fund received a grant from Nestlé Science

Symbols Used	*Explanation*
+	*Positive – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	*Negative – Indicates that these issues have not been adequately addressed.*
⊘	*Neutral – indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
3. Were <u>study groups comparable</u>?	3	Unclear

3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
3.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	No
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Yes
3.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A

4. Was method of handling <u>withdrawals</u> described?	4	Yes
4.1. We**r**e follow up methods described and the same for all groups?	4.1	Yes
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4. Were reasons for withdrawals similar across groups	4.4	Yes
	4.5	N/A

4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?		
5. Was <u>blinding</u> used to prevent introduction of bias?	5	No
5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	No
	5.3	Unclear
	5.4	N/A
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.5	N/A
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?		
5.5. In diagnostic study, were test results blinded to patient history and other test results?		
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Unclear
	6.1	Yes
	6.2	N/A
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.3	Yes
	6.4	Yes
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.5	Unclear
	6.6	N/A
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.7	Yes
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.8	N/A
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?		
6.6. Were extra or unplanned treatments described?		
6.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?		

6.8. In diagnostic study, were details of test administration and replication sufficient?		
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
	7.1	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.2	Yes
	7.3	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.4	Yes
	7.5	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.6	Yes
7.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.7	Yes
7.5. Was the measurement of effect at an appropriate level of precision?		
7.6. Were other factors accounted for (measured) that could affect outcomes?		
7.7. Were the measurements conducted consistently across groups?		
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
	8.1	Yes
8.1. Were statistical analyses adequately described the results reported appropriately?	8.2	Yes
	8.3	Yes
8.2. Were correct statistical tests used and assumptions of test not violated?	8.4	Yes
	8.5	Yes
8.3. Were statistics reported with levels of significance and/or confidence intervals?	8.6	Yes
8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.7	N/A

8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? 8.6. Was clinical significance as well as statistical significance reported? 8.7. If negative findings, was a power calculation reported to address type 2 error?		
9. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?** 9.1. Is there a discussion of findings? 9.2. Are biases and study limitations identified and discussed?	9 9.1 9.2	Yes Yes Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely? 10.1. Were sources of funding and investigators' affiliations described? 10.2. Was there no apparent conflict of interest?	10 10.1 10.2	Yes Yes Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Citation	Vidal-Casariego, A., Calleja-Fernandez, A., Villar-Taibo, R., Kyriakos, G., Ballesteros-Pomar, & D, M. (2014). Efficacy of arginine-enriched enteral formulas in the reduction of surgical complications in head

	and neck cancer: A systematic review and meta-analysis. *Clinical Nutrition, 33*, 951-957. doi:10.1016/j.clnu.2014.04.020
Study Design	Systemic review with meta-analysis
Class	M
Quality Rating	☒ + (Positive) ☐ - (Negative) ☐ ⊘ (Neutral)
Research Purpose	To assess whether arginine-enriched enteral nutrition has an impact on complications and length of stay for head and neck cancer surgery patients.
Inclusion Criteria	• Type of study (randomized, double-blinded, controlled studies) • Language (English or Spanish) • Patient type (head and neck cancer treated with surgery) • Species (human) • Outcomes (complications of surgery, length of stay) • Methodological quality (Jadad scale)
Exclusion Criteria	• Non-randomized studies • Trials that compared two formulas with immunonutrition • Immunonutrition not based on arginine • Studies where complications and length of stay were not measured
Description of Study Protocol	Search Procedure: • Databases: Medline (PubMed), Trip Database, Central (Cochrane Library) • Search Terms: “Head and Neck Neoplasms”, “Head and Neck Cancer”, “Enteral Nutrition”, “Tube Feeding”, “Arginine”, AND/OR “Immunonutrition” Was study quality assessed? Yes, based on inclusion and exclusion criteria as well as Jadad score. All scored 3, 4, or 5. Type of interventions and outcomes investigated: • Intervention: Arginine-based immunonutrition compared to isocaloric and isonitrogenous enteral formula; Immunonutrition was implemented in Pre/Peri, Peri, or Post-operative phases.

	• Outcomes: Postoperative outcomes (fistulas, surgical site infections, other infections) and length of stay. Populations included: Head and neck cancer surgery patients (oral, pharynx, larynx cancers) that met inclusion and exclusion criteria
Data Collection Summary	What type of information was abstracted from articles? • Patient characteristics • Outcomes of interest (fistulas, infections, length of stay) • Immunonutrition timing (pre and post or postoperative) How was it combined? Forest plots What analytic methods were used, if any? Odds ratios and confidence intervals (using Mantel-Haenszel method; heterogeneity assessed with Cochran's Q
Description of Actual Data Sample	Identified: 62 studies Included: 6 studies (total n = 397: 210 immunonutrition, 187 control) • 267 Males 130 Females • Age (Median): 55-63 years old • All participants had either oral, larynx or pharynx cancer with surgical intervention Type of studies used: randomized, double-blinded controlled studies
Summary of Results	Key Findings: • Immunonutrition was associated with shorter hospital stay, likely due to reduction in fistula formation (observed in all 6 studies) • Improvement in wound healing was new to this meta-analysis Other Findings: • Immunonutrition formulas were well-tolerated across studies
Author Conclusion	Arginine-enriched enteral formula may reduce the occurrence of postoperative fistulas and length of stay in the hospital. The current literature suggests post-operative use of these formulas is related to this effect.

Reviewer Comments	• *Review strengths: followed PRISMA methodology; focused on studies that assessed clinical outcomes; assessed optimal timing of immunonutrition, no heterogeneity or publication bias found.* • *Review limitations: Small number of high-quality studies found (6) and only two with maximum Jadad score; poor blinding and randomization noted in trials; small studies included.* *More high-quality trials are needed to understand the impact of perioperative immunonutrition as well as the long-term outcomes and financial impact of these formulas. This further research will allow for better generalizability.*
Funding Source	None

Symbols Used	*Explanation*
+	*Positive – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	*Negative – Indicates that these issues have not been adequately addressed.*
⊘	*Neutral – indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions	
1. Will the answer if true, have a direct bearing on the health of patients?	Yes
2. Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3. Is the problem addressed in the review one that is relevant to dietetics practice?	Yes
4. Will the information, if true, require a change in practice?	Yes

If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.	
Validity Questions	
1. Was the question for the review clearly focused and appropriate?	Yes
2. Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search terms used described?	Yes
3. Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4. Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes
5. Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6. Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7. Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes
8. Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9. Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10. Was bias due to the review's funding or sponsorship unlikely?	Yes
MINUS/NEGATIVE (-)	

If most (six or more) of the answers to the above validity questions are "No," the review should be designated with a minus (-) symbol on the Evidence Quality Worksheet.
NEUTRAL (∅) *If the answer to any of the first four validity questions (1-4) is "No," but other criteria indicate strengths, the review should be designated with a neutral (∅) symbol on the Evidence Worksheet.*
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (must include criteria 1, 2, 3, and 4), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*