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IMMUNONUTRITION FOR PATIENTS UNDERGOING ELECTIVE HEAD AND NECK CANCER SURGERY VS. STANDARD ENTERAL NUTRITION

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Summary. The purpose of this literature review was to examine the most recent scientific evidence on the effect and real benefits of enteral immunonutrition in postoperative recovery compared to standard formulas in patients with head and neck cancer undergoing elective surgery. The main bibliographic sources of high scientific impact have been rescued from databases such as Medline, PubMed, Cochrane Library, Elsevier, Scielo and major medical oncological societies such as: SEOM, NIH and clinical guidelines such as ESPEN. There is great heterogeneity among the results examined in the different reviews and meta-analyses on the effect of immunonutrition on postoperative complications. Overall, the findings indicate a benefit in the use of immunonutrition, however, for head and neck cancer they are based on poor quality evidence due to numerous limitations, so the scientific community has not yet found a common consensus. More prolific research could confirm such results with greater benefits for patient survival and, consequently, a shorter hospital stay, which would burden less on the costs of the healthcare system.

Key words: Head and neck cancer, enteral immunonutrition in cancer, *arginine, fatty acids ω-3*.

INMUNONUTRICIÓN PARA PACIENTES SOMETIDOS A CIRUGÍA ELECTIVA DE CÁNCER DE CABEZA Y CUELLO VS NUTRICIÓN ENTERAL ESTÁNDAR

Resumen. La finalidad de esta revisión bibliográfica ha sido examinar la evidencia científica más reciente sobre el efecto y los reales beneficios, en la recuperación postoperatoria, de la inmunonutrición enteral respecto a las fórmulas estándar, en pacientes que padecen cáncer de cabeza y cuello, sometidos a cirugía electiva. Las principales fuentes bibliográficas de elevado impacto científico, se han rescatado a partir de bases de datos como Medline, PubMed, Biblioteca Cochrane, Elsevier, Scielo y principales sociedades médicas oncológicas como: SEOM, NIH y guías clínicas como ESPEN. Existe una gran heterogeneidad entre los resultados examinados de las diferentes revisiones y metaanálisis, sobre el efecto de la inmunonutrición en las complicaciones postoperatorias. En general, los hallazgos indican un beneficio en

el uso de la inmunonutrición, sin embargo, para el cáncer de cabeza y cuello se basan en evidencia de calidad deficiente por numerosas limitaciones, por lo que la comunidad científica no ha encontrado todavía un consenso común. Una investigación más prolífica podría confirmar tales resultados con mayores beneficios para la supervivencia del paciente y, consecuentemente, una menor estancia hospitalaria, que gravaría menos en los costes del sistema sanitario.

Palabras clave: Cáncer de cabeza y cuello, inmunonutrición enteral en el cáncer, *arginina, ácidos grasos ω-3*.

Introduction

Head and neck squamous cell carcinoma [HNSCC] is the 6th most common cancer in the world. It is very heterogeneous due to the multiplicity of sites and tissues involved, such as epithelial cells of the oropharynx, larynx/hypopharynx, nasal cavity, glands and upper aerodigestive tract (Fig 1). It has a very high incidence, is lethal, aggressive, recurrent with metastases, has a high morbimortality due to postoperative complications and is responsible for approximately 1-2% of all cancer deaths [(1-4)].

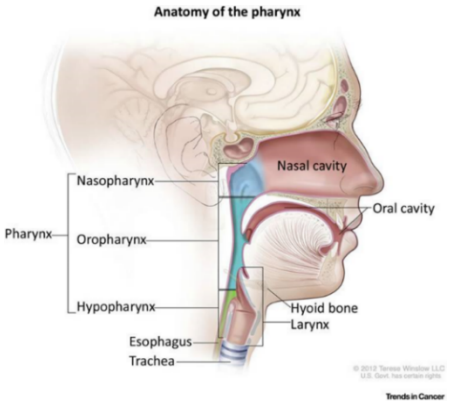

Figure 1. *Localization of cancer of the head and neck. Horton JD 2019* [(4)]

Notwithstanding technological advances over the last 50 years, both in specific treatments and surgical techniques, its overall survival rate remains constant at around 63-66%.

Its risk factors are tobacco, alcohol and *Human Papilloma* Virus (HPV). Its prevalence is higher in the male sex, specifically in Spain it is 10:1 for men, although in recent years, due to the increase in smoking and alcoholism in women, this ratio is being modified [(5)].

During the development and evolution of CECyC, the immune system plays a fundamental role, through the synergistic action of an innate and an adaptive response. Exposure to tumor cells increases the secretion of proinflammatory cytokines, the interleukins (IL-1β, IL-6, TNF-α) and anti-inflammatory cytokines (IL-2, IL-4, IL-10), the latter of which may be affected by poor nutritional status, as is common in the oncology patient or by neoplasia. This condition results in a suppression of the immune system, by a variation of immunocompetent cells, by a dysregulation in the production of pro-inflammatory cytokines and by a consequent intensification of the inflammatory state. The alteration in the antitumor response allows, therefore, the free development of the neoplasm. [(6, 7)]

The combination of the same neoplasm and its specific treatments, consisting of chemo-radiotherapy (CRT) and surgery, has a devastating synergistic effect on the organism, which determines a toxic state with important secondary effects on the integrity of the local tissues The microvascular damage resulting from radiotherapy produces tissue hypoxia, together with fibrosis, as a result of a reparative process due to alteration of the fibroblasts. These factors predispose the patient to local wound infections and complications, the appearance of fistulas and impaired healing, in addition to general

infections and complications (urinary, respiratory). With a cascade mechanism, the clinical picture is critical because of the numerous postoperative complications that lead to high morbidity and mortality (Fig. 2). [8]

Current scientific research is directed towards the use in nutritional support of immunomodulatory enteral formulas (INM) enriched with *arginine, fatty acids ω-3*, , nucleotides, etc. These immunonutrients, with both nutritional and pharmacological action, modulating the inflammatory/immune response could prevent the appearance of complications in the surgical patient and represent a new strategy, more effective than the standard normo or hypercaloric and normo or hyperproteic polymeric formula, to contain the neoplasia and improve the quality of life [12-15] (Table 1).

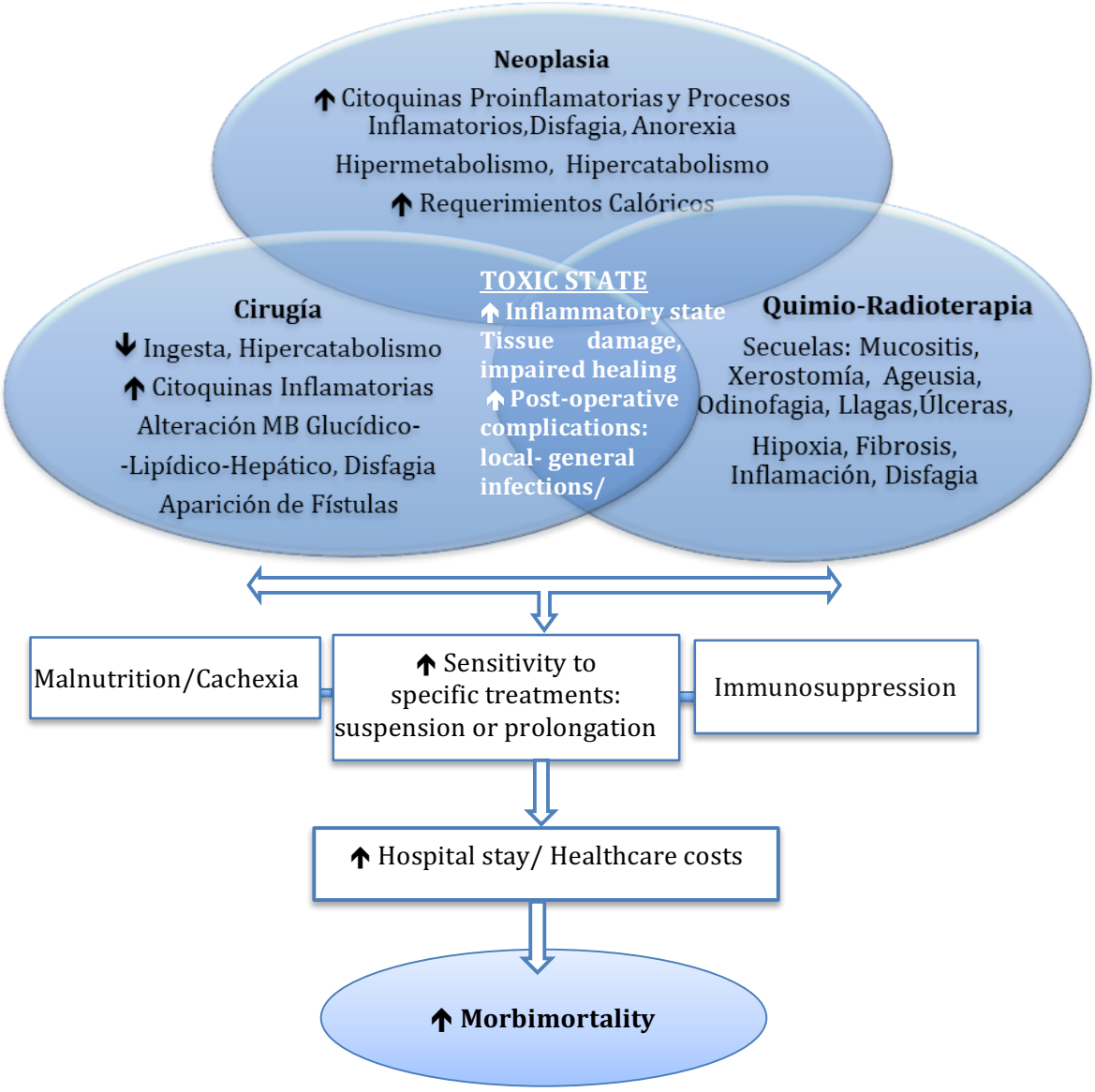

Figure 2. *Synergistic effect between neoplasia, chemoradiotherapy (CRT) and surgery* [3, 5-11, 16-20, 21-24].

The effect of these immunonutrients is coadjuvant: in the reduction of tissue sclerosis, suppressing excessive collagen deposition and in the improvement of wound

healing; in the reduction of inflammation and risk of infection; in reducing esophagitis, diarrhea and weight loss related to toxic effect; in reducing the incidence, severity and occurrence of mucositis during chemotherapy, in the improvement of weight, lean body mass and fat in neoplasms (3, 5-11, 16-20) [3, 5-11, 16-20, 21-24].
It is noted that nutritional optimization represents treatment compliance, improved clinical outcomes and patient rehabilitation [12,15].

Table 1. *Most commonly used pharmaconutrients and their action*

Immunonutrients	Main mechanisms of action
Glutamine	Improves T-lymphocyte response, B-lymphocyte and macrophage function. Improves the function of the intestinal mucosa. Decreases the rate of infections. Decreases hospital stay.
Arginine	Increases T-lymphocyte response. Increases cytokine levels in blood. Increases insulin, prolactin and glucagon secretion.
Fatty acids ω-3	Increases circulating levels of Ig and INF-ɣ. Improves neutrophil function. Increases the percentage of T helper lymphocytes
Nucleotides	Promote DNA and RNA synthesis Improves macrophage activity and lymphocyte function.

Adapted from *Gómez Candela C* et al. (2021) [25]

The possible beneficial effects of immunonutrition in oncological pathologies have been investigated for 30 years. However, it is since 2000 that research activity has intensified. *Gianotti* et al. (2002) [26] were among the pioneers , with a randomized clinical trial in which they evaluated the effect of pre- and perioperative INM compared to the control group with the traditional formula in patients undergoing gastrointestinal surgery. They observed a lower incidence of postoperative infectious complications and a shorter hospital stay (HME) in the two groups with administration.

In addition to determining the clinical benefits, one of the crucial points of the research, is to define the most effective dose, duration and timing of pre-, post- or peri-operative administration of immunonutrients (INM).

Another determining factor to know the real efficacy of each of the immunonutrients is to examine them in isolation, because in a combination of ingredients, as found in the most common commercial formulas, what is observed is a synergistic effect [14].

Mueller et al. (2019) [27] and *Aeberhard C* et al. (2018) [28] observed, in two very similar studies, lower incidence of postoperative infectious complications and as a

consequence a strong reduction of the mean hospital stay (MHS), which actually seemed very excessive in correlation with the preceding data, in the subgroup of intervention with preoperative INM, previous radiotherapy and extensive surgery.

Beneficial effects of INM, both pre- and perioperatively administered, were confirmed in the most current meta-analysis of 24 randomized clinical trials (RCTs) published by *Buzquurz F* et al. (2020) [29], an intense reduction in general and wound infections was observed, however, no impact, in contrast, on mortality. Through a postoperative administration of INM and to better understand the effect, *Casas-Rodera P*. et al. (2008) [30] compared two different INM formulations, in two groups, one with isolated arginine, the other with the *arginine*triad, *ω -3*nucleotides and in the control group the standard formula. No major significant differences or clinical benefits were observed between the two MRI intervention groups.

A 3.5-day reduction in hospital stay was found as a result of postoperative MRI administration in the systematic review by *Stableforth WD* et al. (2009) [31]. This decrease was not very clear because it was not associated with any other clinical benefit.

Vidal-Casariego A. et al. (2014) [32] confirmed in a systematic review- meta-analysis, notwithstanding numerous limitations concerning trials, the beneficial effect of both peri- and postoperative-only MRI, associating it with a significant reduction in the occurrence of fistulas and hospital stay.

Identical to *Casas-Rodera P* et al. (2008) [30], *Barajas-Galindo DE* et al. (2020) [21] who, in a retrospective observational study, did not confirm beneficial effects of postoperative MRI in malnourished patients, but rather related the appearance of fistulas to the degree of malnutrition of the patient.

The first authors to evaluate perioperative supplementation of INM were *Synderman CH* et al. (1999) [33] administered a higher dose of *arginine* than all other studies (18.7 g of *arginine* 5 days before and 12.5 g 8 days after the intervention). In a trial of high methodological quality they observed the reduction of infections, however, they did not point out any impact on the reduction of hospital stay.

Felekis D et al. (2010) [34], like other previous authors, following a perioperative MRI procedure, observed a significant reduction in postoperative complications exclusively in the normo-nourished subgroup. Results supported by *Turnock A*. et al. (2013) [7] a few years later.

Howes N et al. (2018) [35], published a systematic review, collected in the *Cochrane database,* of 19 RCTs, comparing peri- and postoperative NMI. Despite the large number of participants, 1099 in total, the sample size was very limited, ranging from 8 to 209 subjects. In this case, there was no significant evidence that immunonutrition had any real effect on wound infection, postoperative complications, hospital stay, mortality, etc.

The main objective of this review was to analyze the scientific evidence on the validity, effectiveness and real benefit of INM, evaluating the reduction of clinical parameters such as: local/general infections, occurrence of fistulas, mean hospital stay (MSH) and mortality. It will also be convenient to determine the most effective time of administration of the immuno-formula.

Method

A bibliographic review was carried out on the use of immuno-nutrition in the CECyC in the last 20 years, consulting the most important and relevant sources of scientific literature. Research in this area is so limited and muddied, therefore, in order to examine the evolution over time of the studies and gather more information, no restriction or filter of seniority of the last 5 years has been imposed on the provider's search. The preferred elements have been systematic reviews and meta-analyses with a minimum Impact Factor (IF) > 1.5. The literature search began in January 2022 and ended in April 2022. Article eligibility criteria were established (Tables 2 and 3). All trials met the inclusion criteria, except for two trials with specific prior radiotherapy (RT) treatment, included to look at deviation during treatment and to have a broader overview of the question, until the most recent systematic review/meta-analysis in August 2018.

Table 2. *Criteria for selection of articles from the bibliography*

Criteria for inclusion of articles
- Randomized controlled trials, systematic reviews and meta-analyses in humans. - Publications in English and/or Spanish. - Patients ≥ 18 years old diagnosed with head and neck and undergoing elective major surgery. - Any nutritional status: at risk of malnutrition, malnourished or normo-nourished. - Full text" articles or with limited access, consulted through the *sci-hub*web page. - Intervention group: enteral formula enriched with immunonutrients. - Supplementation with arginine-fatty acids ω-3 - RNA in isolation or as a set (oral/enteral Impact® formula). - Control group: enteral formula with traditional nutritional supplementation. - Timing of MRI intervention: pre, post and perioperative. - Postoperative recovery after immunonutrition. - Studies that will evaluate as outcomes general and wound post-surgical infectious complications, occurrence of fistulas, EMH (mean hospital stay) and survival.

Table 3. *Criteria for selection of articles from the bibliography*

Article exclusion criteria
- Non-random EC. - Low level and low IF scientific journals. - Patients aged ≤ 18 years. -Articles with patients who did not suffer from head and neck cancer and who were not undergoing elective surgery. - Studies that, in addition to surgery, included previous chemotherapy treatments previous. - Parenteral nutrition. - Studies with different INM of the arginine-fatty acid triad ω-3 - RNA. - Studies with the use of a placebo in the control group.

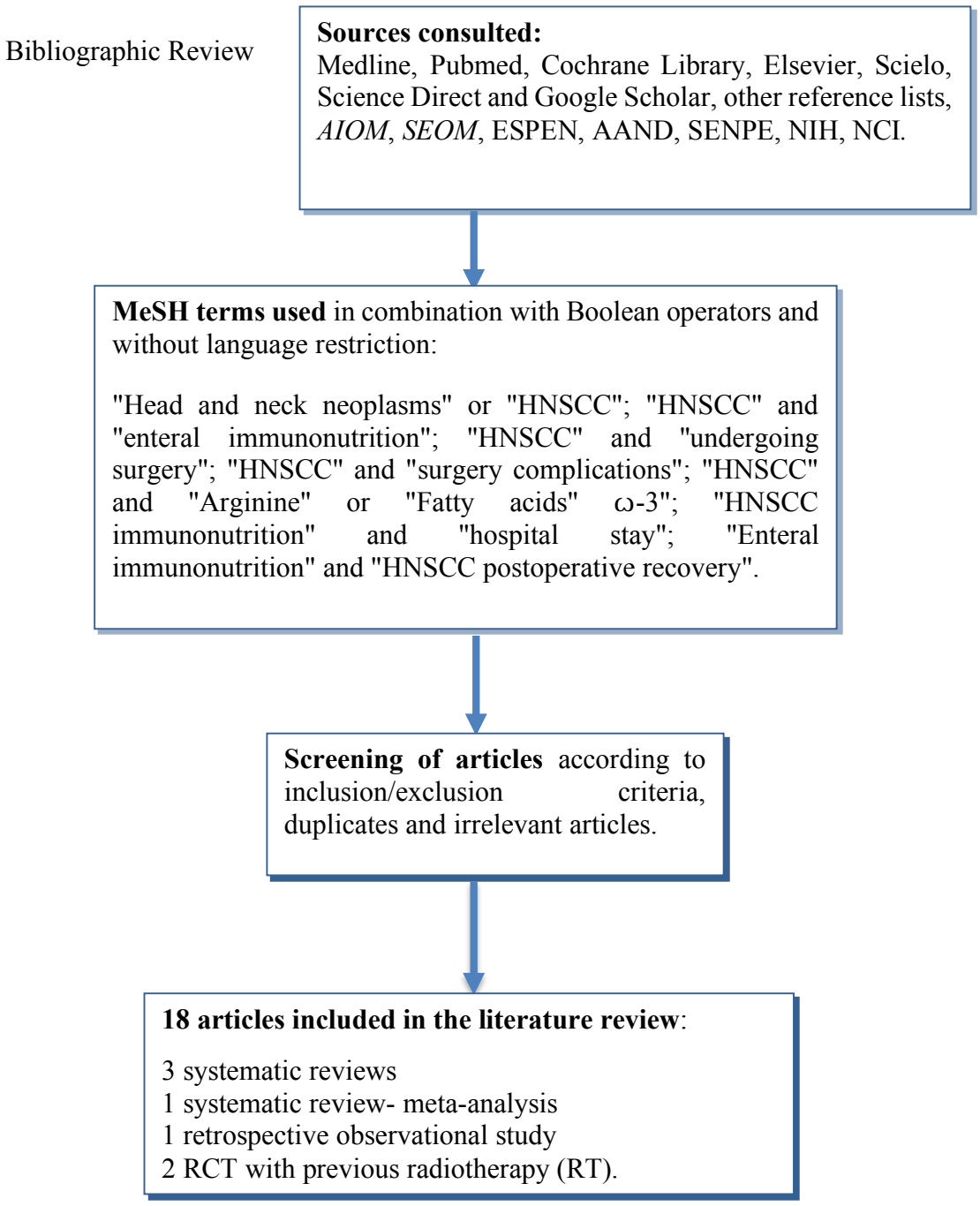

Figure 3. *Flow chart of the literature review*

Results

The reduction in hospital stay of 3.5 days, observed in the postoperative MRI intervention group, in the review by *Stableforth* et al. (2009) [31]) was considered very unclear and was not associated with other clinical benefits. The increase in CD4 and CD4/CD8 lymphocytes determined in only one trial [36] did not, however, correspond to a reduction in hospital stay (HME). A very contrasting analogous result, following

postoperative MRI, was observed by *Synderman CH* et al. (1999) [33]. In the intervention group they evaluated an incongruent decrease in HME corresponding to an increase in both wound infection and fistula occurrence. Increase that the authors related to the surgical technique, to the severity of the pathology and to the nutritional status, or even hypothesized that the cause of this result was due to some adverse effect of the INM (as in septicemic patients) that detrimentally altered the inflammatory response [33].

In spite of the postoperative administration of a formula with a high dose of *arginine*, neither *Barajas Galindo* et al. (2020) [21] found clinical benefits, however, they observed a higher incidence of fistulas in severely malnourished patients in both groups (Table 4), a result related to a low intake of formula received. In addition, hospital stay was not correlated with immunonutrition, on the contrary, with the presence of fistulas that depend on malnutrition.

Vidal Casariego et al. (2014) [32] in contrast (Table 5) in a meta-analysis review confirmed the benefit of postoperative MRI, despite numerous study limitations. They determined a significant reduction of fistulas [37] in addition to a reduction of fistulas and EMH in another trial [38], consolidating the fistula-EMH relationship. No effect on wound infection or other complications, however, was determined.

In contrast to the previous result, in the same review by *Stableforth* et al. (2009) [31] and *Riso S* et al**.** (2000) [36] confirmed that INM administered postoperatively in malnourished patients significantly improved the main postoperative complications and EMH, but did not improve the occurrence of fistula, which had the same incidence in the two groups (Table 4). This could mean, therefore, that INM has no effect on the fistula or that EMH does not depend only on the fistula, a hypothesis that was confirmed by *Luis DA et al*. (2010) [39] in the systematic review by *Casas Rodera* et al. (2012) [40] in a trial with comparison of a high *arginine* dose with another with its half in the two groups, however the limitations were not reported, the blinding was very unclear and the inter-trial variability was, as in other reviews, very high (Table 5).

Both *Aeberhard* C et al. (2018) [28] [28] as *Mueller SA* et al. (2019) [27] observed as a result of a preoperative administration of INM, with prior radiotherapy (RT), a sharp decrease in fistula incidence and an even higher reduction of EMH (from 17 to only 6 days) in high-compliance subgroups. However, they linked the sharp reduction in EMH to the *Swiss DRG 2012* discharge optimization process that penalizes a prolonged stay. They therefore confirmed, in agreement with *Barajas Galindo* et al. (2020) [21], that fistula and HME are dependent on malnutrition, also stressing the importance of high compliance, in addition to the presence of *arginine* (Table 6).

Howes N et al. (2018) [35], have published, in the *Cochrane*database, the most relevant and recent review on immunomodulatory supplementation in patients with CECyC undergoing elective surgery (Table 7); 19 RCTs in total (post and perioperative INM, excluding 3 trial administering other types of immunonutrients). The different timing of administration did not produce significant differences in the findings; however, it was observed that INM given only postoperatively (evaluated in 10 RCTs, n = 747) could reduce the risk of fistula incidence by 50%. EMH was reduced in 8 of 10 studies in which it was analyzed (n = 757) without being able to confirm this finding due to lack of evidence, because INM had no effect on wound infection and on overall complications. Even less was reported any effect of immunonutrients on mortality [35].

Tabla 4 Características de los ensayos clínicos aleatorizados (ECA) con empleo de INM postoperatoria vs nutrición estándar

Autores Tipo de estudio	n Inm/ Est.	Momento de administración INM	Tipología Fórmulas INM/Est.	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Stableforth 2009 [31] Rev. Sist. 10 ECA	Tot. 605	Inm Postoper.	Impact® Enteral:Arginina+ ác. grasos ω-3, ARN Estándar Nutrison Intensive®	Peso, complic. clínicas, parám. bioq., EMH, calidad de vida, tolerancia a fórmula, fuerza de agarre.	↓ EMH se observó en 6 estudios (3,5 días en media), sin otro beneficio clínico que lo explicara ↓ Fístula en 3 ECA, ↓ Infecc. herida en 2 ECA ↑ mejor respuesta inmunol. en sólo 1 ECA, pero sin reducc. de EMH. En 1 ECA ↑Fístula + Infecc. herida con una incongruente ↓ de EMH	ECA muy pequeños. Había poca evidencia de heterogeneidad. Datos insuf. para excluir efecto de INM. Muy ≠ las intervenciones, la duración, el tipo y estadio de los tumores. Comparación INM perioper. vs NO+ postoperatoria. Falta de datos sobre tolerancia a la fórmula. Limitaciones metodológicas. Sólo la mitad de los estudios informaron del doble cegamiento [31].

Autores Tipo de estudio	n Inm/ Est.	Momento de administración INM	Tipología Fórmulas INM/Est	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Barajas Galindo 2020 [21] Estudio Obs. Retrosp.	Tot 135 INM 68 EST 67	Inm Postoper.	Impact® [Polim +arg+ ác. g.ω3 + RNA] Ingesta de arginina= 21,5g	Fístulas, EMH, reingresos y la mortalidad a 90 días	Ningún resultado significativo, con elevada dosis de arginina, después de ajustes. Fístula: > incidencia en desnutridos de ambos grupos. Posible relación entre: Desnutrición -fístula - EMH	Estudio retrospectivo, pacientes de ≠ épocas y probablemente ≠ técnicas quirúrgicas. Bajo cumplimiento de la ingesta media en el 20,6% de los participantes. No inclusión de datos sobre la tolerancia al alimento (diarrea) o análisis sobre la rentabilidad [21].

Origen: Datos recopilados de Stableforth 2009 [31], Barajas Galindo 2020 [21] n = muestra; Inm = Fórmulas Inmunomoduladoras; Est.= Fórmula Estánd

Tabla 5 Características de los ECA con empleo de INM peri/postoperatoria vs nutrición estándar

Autores Tipo de estudio	n Inm/ Est.	Momento de administrac. Inm	Tipología Fórmulas Inm/Est.	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Casas Rodera 2012 [40] Rev. Sist. 14 ECA	Tot. 836 INM 436 EST 400	Inm Peri/Postoper.	-Polim+arginina -Impact® [Polim +arg+ ác. g.ω3 + RNA]	Complic. inf herida, EMH, parám bioq. tolerancia a fórmula.	↓ EMH En 6 ECA ↓ Fístula en 5 ECA, ↓ Infecc. herida En 2 ECA ↓Complicac.post. en 2 ECA En 1 ECA ↑Fístula e Infecc. herida No ≠ en marcadores nutricionales e inmunológicos EMH no depende solo de la fístula	No reportadas las limitaciones de estudios. Cegamiento poco claro Elevada heterogeneidad entre ensayos [40].

Autores Tipo de estudio	n Inm/ Est.	Momento de administrac. Inm	Tipología Fórmulas Inm/Est.	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Vidal-Casariego A. 2014 [32] Rev. Sist./Metaan 6 ECA doble ciego	Tot.397 INM 20 EST 187	Inm Peri/ Postoper.	-Polim+arginina -Impact® [Polim +arg+ ác. g.ω3 + RNA]	Fístulas, inf. de heridas y generales EMH	Beneficio de INM postoperatoria ↓ EMH y Fístulas en 1 ECA ↓ Fístula en 2 ECA No ≠ en complic infecciosas, ni en tolerancia a INM. Posible relación Fistula-EMH	Elevada variabilidad entre los ECA por ≠ de tipología del cáncer, bajo nº de ECA y baja calidad de algunos, déficit en el método de aleatorizado y de cegamiento de las intervenciones. Tamaño de muestra pequeño, bajo poder estadístico, no hubo heterogeneidad estadística entre los ECA. Comparación de ≠ momento de administración vs nutrición estándar y ≠ dosis de arginina 12-20 g/L empleada, fórmula INM especificada en sólo 3 ECA. Estado nutricional muy ≠ en el reclutamiento [32].

Origen: Datos recopilados de *Casas Rodera* 2012 [40] *Vidal-Casariego A.* 2014 [32] n= muestra; Inm = Fórmulas Inmunomoduladoras; Est.= Fórmula Estándar

Tabla 6 Características de los EC, con radioterapia previa, incluidos en la revisión bibliográfica sobre el empleo de INM preoperatoria vs nutrición estándar

Autores Tipo de estudio	n Inm/ Est.	Momento de administrac. Inm	Tipología Fórmulas Inm/Est.	Objetivos	Resultados en grupo de intervención INM	Limitaciones
Aeberhard C 2018 [23] ECA no aleatorizado + Radioterapia previa	Tot 411 INM 202 EST 209	Inm Preoperat	Oral Impact® [dosis diaria arg. = 11,3g; ω-3= 3g	Complicaciones quir. EMH, mortalidad y fistula en pacientes sometidos a C(RT) previa y cirugía	↓ Fístula en grupo INM ↓EMH resultado sólido- después de ajuste multivar. Beneficios significativos en subgrupo de alto cumplimiento (al menos 75% de la ingesta prescrita) y con RCT y cirug. extensa No ≠ en complicaciones gener. Relación entre: Desnutrición - Fistula - EMH	Estudio no aleatorio, carácter retrospectivo de la recogida de datos. ≠ en cuanto a variables sociodemográficas, sitio, estadio tumoral y tipo de cirugía entre los 2 grupos y con RCT previa. Proceso de alta hospitalaria específico *Swiss DRG 2012* ha podido influir en EMH (por penalizar una estancia prolongada) [23].
Mueller SA 2019 [22] ECA + Radioterapia previa	96 INM 51 EST 45	Inm Preoperat.	Oral Impact® Arginina + ác. grasos ω-3, ARN oral /enteral	Complicaciones de la herida en general. EMH en pacientes sometidos a (RCT) y cirugía	↓ Complic. generales de la herida ↓ EMH reducción muy intensa (de 17 a 6 días) en pacientes de alto cumplimiento Relación entre: Desnutrición - Fistula - EMH	Tamaño pequeño de la muestra. Carácter retrospectivo del ECA. Probable sesgo por la optimización del proceso de alta hospitalaria SwissDRG en 2012 [22].

Origen: Datos recopilados de Aeberhard C, 2018 [23], Mueller SA, 2019 [2]2 n= muestra; Inm = Fórmulas Inmunomoduladoras; Est.= Fórmula Estándar

Tabla 7 Características de los ECA con empleo de INM peri/postoperatoria vs nutrición estándar [35]

Autores Tipo de estudio	n Inm/ Est.	Momento de administración Inm	Tipología Fórmulas Inm/Est.	Objetivos	Resultados en grupo de intervención Inm	Limitaciones
Howes N, 2018 [35] Revisión Sistem. 19 ECA 2 ECA excluidos por ≠ fórmulas INM	Tot. 1099	19 ECA: -10 ECA postop - 9 ECA periop	- Polimér.+ arginina Impact® - Polimér + arginina Nutrison intensive® - Impact Recover®+ arg+ glutam. ARN	1º EMH infección de la herida, formación de fistulas, tolerancia a la fórmula INM 2º: mortalidad por infecciones y complicaciones	Fístula ↓ del 50% de incidencia con INM postoperatoria. Evaluado en 10 ECA (n=747). ↓ EMH: Se redujo en 10 ECA (n=757) con reducción de 2,5 días, sin encontrar pruebas; Infección herida: evaluada en 12 ECA (n=812). No evidencia de un efecto de la INM sobre la infección de la herida Mortalidad: Se evaluó en 14 ECA (n= 776). Complicaciones generales: No se reportaron con frecuencia complicaciones infecciosas generales. INM puede tener poco o ningún efecto sobre heridas, mortalidad y EMH	Según la calificación GRADE: ↓ EMH evidencia baja ↓ Infección de la herida y mortalidad con evidencia muy baja. Estudios y el tamaño de muestra pequeño (12/19 ECA con n < de 25 participantes), IC muy amplio en torno a estimaciones del efecto, descripción muy insuficiente del método para evaluar los resultados (evaluación de la herida y efectos adversos). Resultados incompletos y no confiables. Elevada heterogeneidad en dosis, tipología de la fórmula y duración de administración INM (de 5 a 14 días preoperatoria y de 5 a 22 ± 12 días perioperatoria). Elevada variabilidad entre estudios [35].

Origen: Datos recopilados de *Howes N, 2018 [35]* n = muestra; Inm = Fórmulas Inmunomoduladoras; Est.= Fórmula Estándar

Discussion and conclusions

The use of immunonutrients as a new strategy to contain head and neck cancer neoplasia in patients undergoing elective surgery presents considerable perplexities. There is an inconsistency between the use of immuno-modulating formulas and the results, which are very contrasting, scarce and incomplete due to lack of evidence and a high number of limitations. It is not possible to confirm the strength of the evidence of its

real benefits. Evidence so necessary in order to evaluate the cost-effectiveness of this intervention and to decide whether it is convenient to sustain the huge daily cost of drug-nutrition, versus a possible reduction of treatments, of a patient's hospitalization and an improvement in his or her quality of life, which is clinically and economically important [35].

Casas-Rodera P. et al. [30], in their trial demonstrated that the immunonutrient triad had no greater potential than the administration of arginine alone. More determinant in the postoperative recovery of the patient was, according to the authors, the nutritional status and the surgical technique, with respect to the impact that INM could have.

According to the *GRADE* (Grade of Recommendation, Assessment, Development, and Evaluation) rating of the evidence of effect on the actual benefit of immunonutrition, in the review by *Howes N* et al. (2018) [35]), ranged from low (for reduction of EMH and fistula occurrence) to very low (for reduction of wound infection and mortality), attributable to a high number of limitations that analogously characterize most clinical trials evaluated in this setting and are summarized in Table 8. Numerous biases attributed to the very wide confidence interval, to the high heterogeneity, revealed in the type of formula, with *arginine* administered alone or in a set of immunonutrients and corresponding doses, methodology and scientific quality of the studies, which varied from low to very low according to the *Grade System*rating.

Limitations, in addition, on the representativeness of the sample, such as its size and the age of the individuals. There was a large difference in the mean age of the participants in the different studies, which ranged from 47 to 66 years, however, in the trial by *Turnock A* et al. (2013) [7] ranged from 28 to 68 years in the intervention group and from 17 to 79 years in the control group. Likewise, women were underrepresented in the vast majority of the trials, as CCSCC is a predominantly male type of cancer, currently with a reversal of the trend due to an increase in smoking among women; the ratio of men to women in the trials was 65: 7.

A limitation present in many trials is the lack of communication or the coexistence of different nutritional states at the time of recruitment, which complicates, therefore, the comparison of effects and results. Knowing the previous nutritional status could be the main condition for the subsequent development of fistula or other complications, which highlights the importance of nutritional assessment prior to surgery in patients with head and neck tumors [16, 41].

The *American Academy of Nutrition and Dietetics* (*AAND 2019***)** speaks out *in favor of fatty acids ω-3*, *when dietary intake is inadequate, to stabilize body weight and limit body weight loss*, with recommendation grade: strong; imperative and with grade C for S&C cancer [42].

The *Australian Guidelines* (2020) [43] with grade C state that drug-nutrition, in the preoperative period, has no benefit compared to conventional nutrition, however, it is suggested in the postoperative period to reduce the average hospital stay (with grade B recommendation), without having a clear mechanism and evidence on the reduction of complications and infections. Its use should last at least 7 days (grade C).

The *European Society for Clinical Nutrition and Metabolism Guidelines (ESPEN* 2017), on the other hand, suggest the use of fatty acids ω-3 with low level of evidence and grade of recommendation in patients with advanced cancer, undergoing chemotherapy and at risk of malnutrition. There is still insufficient evidence to recommend its use in ECCC [42, 43].

Definitely, it is not possible to trust the results and neither is it possible to attribute them with certainty to immunomodulatory formulas, since they are scarce, contrasting and with a low or very low level of evidence, which shows that this subject is still under development. Scientists do not yet agree on a common consensus on the real efficacy of immunomodulatory enteral formulas administered preoperatively in ECCC. [27,28].

However, according to some studies, administered postoperatively, they could reduce the average hospital stay, because they are probably related to a lower incidence of fistulas, although the mechanism is not very clear because it has not yet been demonstrated [21,31,35]. It is also considered that perioperative supplementation of fatty acids ω-3 may be desirable in malnourished cancer patients or those at risk of malnutrition exclusively for the maintenance of lean mass and weight [44].

Table 9. *Main limitations and sources of clinical heterogeneity in the trials evaluated*

Category	Item	Specification
Study variables	Methodology	Retrospective studies with lack of access to data, low methodological rigor and quality, variability between studies, incomplete and contrasting results, very wide confidence interval (CI) including null value, insufficient communication of methodology and blinding.
	Sample	Non-representative: due to a very wide age range, disproportionate ratio between the sexes of the participants, inappropriate size of the study population, and high heterogeneity of the variables among the participants.
Nutritional intervention	INM Formula	≠ INM formula typology: nutrients administered in isolation or in a triad (nucleotides, arginine, ω-3). ≠ Timing of formula administration: pre, post or perioperative, differences also in the comparison between perioperative administration in the intervention group vs standard postoperative in the control group. ≠ Duration of treatment. ≠ Formulation mode of administration: oral/enteral. ≠ Immunonutrient doses among trials in the same literature review.
Patient	Neoplasia	≠ Typology and clinical stage of the neoplasm considered. Lack of data communication. ≠ Typology of surgery. ≠ Patient severity.
	Nutritional status	≠ Nutritional status among participants [well nourished, moderately/severely malnourished]. ≠ Nutritional status assessment tool used (NRS 2002, VGS-GP, MUST, MNA). ≠ Average intake of each individual participating in the trial or lack of data on the volume received with respect to the indicated volume.
	Follow-up and discharge hospital	≠ Criteria for hospital discharge. Different duration of follow-up of a participant: until hospital discharge, after 30 days or for a few months.

Determinations	Nutritional Assessment Tool	≠ Nutritional status assessment tool used in the studies (NRS 2002, VGS-GP, MUST, MNA).
	Biochemical parameters	≠ Analytical parameters used to assess inflammatory status, immune response or nutritional status and also determined at different times.

Table adapted from *Gómez Candela C,* 2021 [34]. Data collected from references [21-23, 31, 32, 32, 35, 40]

A high percentage of oncology patients, between 35% and 66% approximately, present pathology-related malnutrition at the time of diagnosis [20]. Although it is not yet possible to propose exact and clear recommendations on the use of immunonutrients, the strength of research in this area is the attention and importance given to the need for the attention and importance given to the need for screening and evaluation of the nutritional status of the oncological patient undergoing surgery. In addition to the need to examine the volume of formula intake in relation to the amount of formula supplied, since a relationship has been observed between malnutrition and the appearance of fistulas and, consequently, an increase in hospital stay supplied, since a relationship has been observed between malnutrition and the appearance of fistulas and, consequently, an increase in hospital stay. The aim is to achieve early nutritional treatment that is adequate to their needs, in order to avoid malnutrition, which is associated with a worse clinical prognosis that compromises patient survival [45, 46] and is a burden on health care costs.

Recommendations for future research

Among the recommendations, the main one is the design of an "*ad hoc"* study with high methodological quality, low variability, a very narrow confidence interval and adequate blinding. A prospective nature will be necessary to avoid unavailability of necessary data. Thus, a representative sample with an appropriate size, fair sex ratio and adequate age range. The effect of each isolated immunonutrient will be evaluated, thus avoiding masking. In addition, it will be essential to standardize in the assays parameters such as nutritional status and the tool for its evaluation, immunological/biochemical parameters and the specific time of their determination, as well as the type of formula used, dosage, time and duration of its administration. On the other hand, *follow-up*time, hospital discharge criteria and, finally, the type of cancer, surgery, clinical stage and severity of the participants will be standardized.

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