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Immunonutrition for patients undergoing surgery for head and neck cancer (Review)

Howes N, Atkinson C, Thomas S, Lewis SJ

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Immunonutrition for patients undergoing surgery for head and neck cancer.
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[Intervention Review]

Immunonutrition for patients undergoing surgery for head and neck cancer

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ABSTRACT

Background

Patients with head and neck cancer are often malnourished. Surgery for such cancers is complex and may be undertaken after a course of radiotherapy. As a result, patients may have postoperative complications such as fistulae and wound infections, as well as more generalised infections such as pneumonia. One possible way to enhance recovery, and reduce the incidence of these complications, is by improving nutrition. Nutritional formulas that deliver basic nutrients as well as amino acids (arginine and glutamine), ribonucleic acid (RNA) and/or lipids (omega-3 fatty acids) are known as immunonutrition.

Objectives

To assess the effects of immunonutrition treatment, compared to standard feeding, on postoperative recovery in adult patients undergoing elective (non-emergency) surgery for head and neck cancer.

Search methods

The Cochrane ENT Information Specialist searched the ENT Trials Register; Central Register of Controlled Trials (CENTRAL); PubMed; Ovid Embase; CINAHL; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 14 February 2018.

Selection criteria

We included randomised controlled trials (RCTs) comparing immunonutrition given either preoperatively, postoperatively or perioperatively to adult patients (18 years of age or older) undergoing an elective surgical procedure for head and neck cancer, compared with a control group receiving either standard polymeric nutritional supplements or no supplements.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. The primary outcomes were: length of hospital stay (days), wound infection, fistula formation and adverse events/tolerance of feeds, as defined by trial authors. Secondary outcomes were: all-cause mortality and postoperative complications (as defined by trial authors). We used GRADE to assess the quality of the evidence for each outcome; this is indicated in *italics*.

Main results

We included 19 RCTs (1099 participants). The mean age of participants ranged from 47 to 66 years. Most studies (12/19) had fewer than 25 patients in each treatment group. Most studies (16/19) used immunonutrition formulas containing arginine, but there was variation in the actual products and amounts used, and in the length of intervention postoperatively. Follow-up time for outcome measurement varied considerably across studies, ranging from five days to greater than or equal to 16 months.

Primary outcomes

We found no evidence of a difference in the length of hospital stay (mean difference -2.5 days, 95% confidence interval (CI) -5.11 to 0.12; 10 studies, 757 participants; *low-quality evidence*). Similarly, we found no evidence of an effect of immunonutrition on wound infection (risk ratio (RR) 0.94, 95% CI 0.70 to 1.26; 12 studies, 812 participants; *very low-quality evidence*). Fistula formation may be reduced with immunonutrition; the absolute risks were 11.3% and 5.4% in the standard care and immunonutrition groups, with a RR of 0.48 (95% CI 0.27 to 0.85; 10 studies, 747 participants; *low-quality evidence*). We found no evidence of a difference in terms of tolerance of feeds ('adverse events') between treatments (RR 1.33, 95% CI 0.86 to 2.06; 9 studies, 719 participants; *very low-quality evidence*).

Secondary outcomes

We found no evidence of a difference between treatments in all-cause mortality (RR 1.33, 95% CI 0.48 to 3.66; 14 studies, 776 participants; *low-quality evidence*). Other postoperative complications such as pneumonia and urinary tract infections were not commonly reported.

Authors' conclusions

The risk of postoperative fistula formation may be reduced with immunonutrition, but we found no evidence of an effect of immunonutrition on any of the other outcomes that we assessed. The studies included in this review were generally small or at high risk of bias (or both). We judged the overall quality of the evidence to be *low* for the outcomes length of hospital stay and all-cause mortality, and *very low* for wound infection and adverse events. Further research should include larger, better quality studies.

PLAIN LANGUAGE SUMMARY

Immunonutrition for patients undergoing surgery for head and neck cancer

Review question

This review compared how people recover after surgery for head and neck cancer if they have been given either 'immunonutrition' or a standard feed before and after or only after the surgery. We looked at how long people stayed in hospital, whether they had any complications and how many people in each treatment group died.

Background

Head and neck cancer surgery usually means surgery to treat cancer of the mouth, throat or larynx (voice box). The surgery is complicated and people often experience problems such as wound infections and wound breakdown, as well as infections such as pneumonia. These can lead to a longer stay in hospital. Specific nutrients, for example amino acids (found in protein-based foods), omega-3 fatty acids (often found in fish oils) and nucleotides (found in many foods) have been investigated for their role in helping people recover from surgery. When any of these specific nutrients are added to the patient's feed it is called immunonutrition. We wanted to see whether feeding people immunonutrition improved recovery (for example, led to a shorter length of stay and fewer complications) when compared with a standard feed.

Study characteristics

We included 19 studies that recruited 1099 adults in total (studies ranged in size from 8 to 209 participants, but most (12 out of 19) had fewer than 25 participants per treatment group). The studies focused on people who were given immunonutrition or a standard feed before and after or only after their surgery. The studies varied in the length of time over which people were given the feeds, but this was usually at least five days. The evidence is current to February 2018.

Key results

We did not find evidence of a difference in the length of hospital stay but there was wide variation between the individual studies in what they showed. We found some evidence that people who had immunonutrition may be about half as likely to have breakdown of their surgical wound called a fistula (a channel between the inside of the throat and the surface skin). We found no evidence that immunonutrition had any effect on wound infection (but not all studies were clear in how they measured this) or death. Study feeds were generally well tolerated and there was no evidence of a difference in adverse events such as diarrhoea between treatment groups. Other clinical complications such as pneumonia and urinary tract infections were not commonly reported, but there was little evidence of a reduction with immunonutrition.

Quality of the evidence

Most studies included in this review were small and poorly reported, which means that their results may be less reliable. More studies are needed that are larger, of better quality and conducted within current healthcare systems.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Immunonutrition compared to standard care for patients undergoing surgery for head and neck cancer

Patient or population: patients undergoing surgery for head and neck cancer
Setting: hospitals (international)
Intervention: immunonutrition
Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	Risk with immunonutrition				
Postoperative length of hospital stay (days) Follow-up: 8 to 90 days post surgery or hospital discharge	The mean of reported length of hospital stay (mean values) across the standard care groups was 27.0 (17.4 to 36.1) days	The mean of reported length of hospital stay (mean values) across the immunonutrition groups was 23.2 (15.3 to 31.1) days	MD 2.5 lower (5.11 lower to 0.12 higher)	757 (10 RCTs)	⊕⊕◯◯ LOW[1]	There may be a reduction in the length of hospital stay of 2.5 days with immunonutrition, but the estimate is imprecise (wide CI) and includes the null value
Wound infection Follow-up: 8 to 90 days post surgery or hospital discharge	Study population		RR 0.94 (0.70 to 1.26)	812 (12 RCTs)	⊕◯◯◯ VERY LOW[1,2]	Immunonutrition may have little or no effect on wound infection, but the evidence is very uncertain
	145 per 1000	136 per 1000 (101 to 182)				
Fistula formation Follow-up: 8 to 90 days post surgery or hospital discharge	Study population		RR 0.48 (0.27 to 0.85)	747 (10 RCTs)	⊕⊕◯◯ LOW [1]	There may be an approximate halving of the risk of fistulae formation but the evidence is of low quality
	113 per 1000	54 per 1000 (31 to 96)				

Adverse events/tolerance of feeds Follow-up: 10 to 90 days post surgery or hospital discharge	Study population		RR 1.33 (0.86 to 2.06)	719 (9 RCTs)	⊕○○○ VERY LOW[1,3]	There may be little or no difference in adverse events such as diarrhoea between the treatment groups, but the evidence is very uncertain
	91 per 1000	121 per 1000 (78 to 188)				
All-cause mortality Follow-up: 30 days to greater than or equal to 16 months post surgery	Study population		RR 1.33 (0.48 to 3.66)	776 (14 RCTs)	⊕⊕○○ LOW[1]	Immunonutrition may have little or no effect on mortality.
	18 per 1000	24 per 1000 (9 to 67)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __MD:__ mean difference; __RCT:__ randomised controlled trial; __RR:__ risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by two levels for imprecision: most studies had small sample sizes and confidence intervals around the summary estimates were wide.
[2]Downgraded by one level for risk of bias: assessment of wound infection was poorly reported across studies.
[3]Downgraded by one level for risk of bias: assessment of adverse events was poorly reported across studies and not all studies measured the same adverse events.

BACKGROUND

Description of the condition

The term 'head and neck cancer' encompasses several sites including oral and laryngeal cancers. In 2014, over 11,000 people in the UK were diagnosed with cancers at these sites (Cancer Research UK). Surgical treatment of head and neck cancer can be aggressive and highly complex, and people undergoing these surgeries may have a 30% to 60% incidence of postoperative complications including wound infections and other infections such as pneumonia (Kucur 2015; McMahon 2013; Perisanidis 2012; Yang 2014). This substantial morbidity has inevitable implications for both patients and healthcare systems. Furthermore, a recent systematic review and meta-analysis showed that postoperative complications, especially infections, adversely affect long-term survival (Pucher 2014).

Many patients with head and neck cancer are malnourished for a number of reasons including mechanical obstruction, tumour-induced cachexia, poor dietary habits and excessive alcohol consumption. Poor nutrition is known to have an adverse impact on outcome in this patient group (van Bokhorst 2000). These patients have well-documented immune defects including T-lymphocytopenia and dysfunction, and reduced monocyte HLA-DR expression (Hadden 1997). These defects, combined with the immune suppressive effects of surgery, may contribute to increased postoperative complications such as poor wound healing and sepsis.

Description of the intervention

Nutrition supports immune function by preventing or reversing immunosuppression related to malnutrition. Standard commercial nutritional supplements are described as polymeric, which means they contain whole protein, partially digested starch and triglycerides, along with electrolytes, trace elements and vitamins. More recently, specific nutritional components have been combined with standard polymeric enteral feeds with the aim of specifically improving immune function. Immunonutrition describes enteral feeding formulas usually supplemented with combinations of the amino acids arginine or glutamine, omega-3 fatty acids and nucleic acids. Animal models and human studies have suggested that the individual components have beneficial (or potentially beneficial) effects on immune function. There is evidence that nutritional supplements with immunonutritional additives can favourably modulate the immune and inflammatory response both *in vitro* and in patients with trauma, burns or those undergoing gastrointestinal surgery (Di Carlo 1999; Wu 2001; Zhang 2012). Meta-analysis suggests that immunonutrition reduces infectious complications in critically ill patients (Heyland 2001). They are usually given in liquid form and are designed to provide a patient's 'complete' nutritional requirements, provided they are given in an appropriate volume. Immunonutrition and standardised commercial nutrition supplements may be given either orally or via an enteral feeding tube.

How the intervention might work

The most studied nutrients in immunonutrition formulas are arginine, glutamine, omega-3 fatty acids and nucleotides. Arginine is the most common immunonutrient given to patients with head and neck cancer. It is a non-essential amino acid with a role in the synthesis of nucleotides, polyamines, nitric oxide and proline. Arginine may stimulate lymphocyte function and improve wound healing. Glutamine, also an amino acid, is a fuel for rapidly dividing cells in the body, in particular for enterocytes and colonocytes. The addition of omega-3 fatty acids to enteral nutrition feeds reduces proinflammatory mediators in stressed patients and may reduce infections. The content of each immunonutrition formula varies between products. The biochemical and physiological properties of nutrients included in immunonutrition formulas have been discussed in detail (Worthington 2011).

Why it is important to do this review

Commercial enteral feed products containing specific nutritional components that may favourably affect immune function have been designed to improve the outcomes in surgical patients. Studies of head and neck cancer patients receiving immunonutrition in the perioperative period have not conclusively demonstrated benefit. We carried out a systematic review of randomised controlled trials, which was published in 2009, to determine whether perioperative immunonutrition has a role in the treatment of head and neck cancer (Stableforth 2009). In that review we examined 10 trials investigating the effects of immunonutrition in patients treated surgically for head and neck cancer. A reduction in the length of postoperative hospital stay was seen, but the reason for this reduction was not clear. Most trials were too small to provide precise estimates of intervention effects. There were insufficient data to exclude substantial effects of immunonutrition on clinical outcomes or biochemical and immunological parameters. Since the publication of that review in 2009 there have been further studies that merit evaluation and inclusion in an updated review (Azman 2015; Casas-Rodera 2008; De Luis 2009; De Luis 2014; Falewee 2014; Felekis 2010; Ghosh 2012; Hanai 2018; Sorensen 2009; Turnock 2013).

OBJECTIVES

To assess the effects of immunonutrition treatment, compared to standard feeding, on postoperative recovery in adult patients

undergoing elective (non-emergency) surgery for head and neck cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including quasi-randomised trials. We had planned to subject quasi-randomised trials to a sensitivity analysis (see Sensitivity analysis). We included studies irrespective of language or publication status.

We excluded non-randomised studies, such as cohort studies, because of the increased potential for bias. We also excluded cross-over trials as this methodology is not suitable for evaluating an intervention that must be given at a specific time point.

Types of participants

We included all adult patients (18 years of age or older) undergoing an elective surgical procedure for head and neck cancer under a general anaesthetic.

Types of interventions

Intervention

The intervention was polymeric nutritional supplements with immunonutritional additives given by an oral or enteral route. In order to be included, studies needed to administer the immunonutrition either preoperatively or postoperatively or both pre- and postoperatively. Co-intervention with other oral or parenteral substances was permitted as long as the dose of immunonutritional additives was quantified. The content of each immunonutrition formula can vary between products and we recorded the product used and its contents for each study.

Control

The control group received either standard care (intravenous fluids) and/or polymeric nutritional supplements.

The comparison was:

- immunonutrition *versus* standard care (intravenous fluids) and/or polymeric nutritional supplements.

Types of outcome measures

We assessed the following outcomes in this review, but we did not use them as a sole basis for excluding studies.

Primary outcomes

- Length of hospital stay: measured in days from the day of surgery to discharge from hospital.
- Wound infections: as measured by the proportion of patients in whom any type or degree of wound infection was recorded, at any point postoperatively.
- Fistula formation: as measured by the proportion of patients in whom a fistula was recorded at any point postoperatively.
- Adverse events/tolerance of feeds, as defined by trial authors: as measured by the proportion of patients in whom adverse events relating to tolerance of feed was recorded, at any point postoperatively.

Secondary outcomes

We assessed the following secondary outcomes, measured postoperatively:

- All-cause mortality: as measured by the proportion of patients recorded as having died at any point postoperatively.
- Postoperative complications, as defined by trial authors: as measured by the proportion of patients in whom any type or degree of complication (other than wound infection, fistula formation or relating to tolerance of feed) was recorded, at any point postoperatively.

Search methods for identification of studies

The Cochrane ENT Information Specialist conducted systematic searches for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions. The date of the search was 14 February 2018.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Trials Register (searched 14 February 2018);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (searched via CRS Web 14 February 2018);
- PubMed (1946 to 14 February 2018);
- Ovid EMBASE (1974 to 14 February 2018);
- Ovid CAB Abstracts (1910 to 14 February 2018);
- EBSCO CINAHL (1982 to 14 February 2018);
- LILACS, lilacs.bvsalud.org (searched 14 February 2018);
- KoreaMed (searched via Google Scholar 14 February 2018);
- IndMed, www.indmed.nic.in (searched 14 February 2018);
- PakMediNet, www.pakmedinet.com (searched 14 February 2018);
- Web of Knowledge, Web of Science (1945 to 14 February 2018);
- ClinicalTrials.gov (searched via the Cochrane Register of Studies 14 February 2018);

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), www.who.int/ictrp (searched 14 February 2018);
- ISRCTN, www.isrctn.com (searched 14 February 2018).

The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources

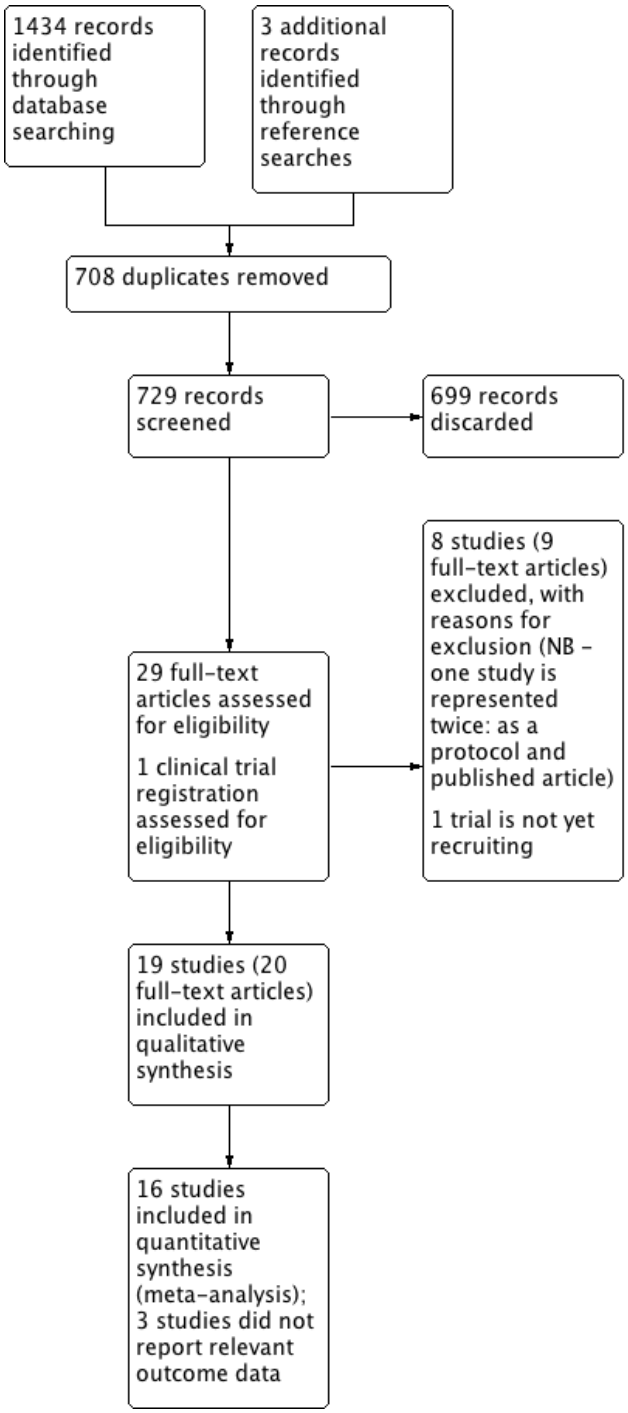
We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, the Information Specialist searched PubMed to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Information Specialist also ran non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

Data collection and analysis

Selection of studies

Two review authors independently examined the titles and abstracts of studies identified through the search strategy (either NH and ST or CA and SJL). Inconsistency between review authors regarding articles for full-text reading was resolved by consultation with another review author. We obtained full-text papers for all studies that could not be excluded on the basis of title and abstract. The same review authors then independently refined their selection by examining the selected articles and excluding those not relevant to this review. The review authors recorded agreement on study inclusion and resolved disagreement by consensus. We contacted original study authors where further clarity was needed in order to select a study for inclusion. We documented decisions on all studies and these are presented in the PRISMA flow chart (Figure 1).

Figure 1. Process for sifting search results and selecting studies for inclusion.



Data extraction and management

We minimally modified a data extraction form from the original provided by Cochrane. Three authors (NH, ST and SJL) tested this on several studies selected for inclusion, and revised it for ease of extraction and to include further useful data items. Two authors (NH and ST) independently extracted data from each study. The review authors were blinded to each other's data.

We extracted data regarding participant demographics, participant disease status, surgical procedures, control group postoperative care and the intervention (frequency and duration of supplementary feeding). SJL and CA combined the tabulated data and checked it for inconsistency.

Assessment of risk of bias in included studies

Two review authors (ST and NH) independently assessed risk of bias. Disagreements were resolved by discussion and consensus, in which the other authors (CA, SJL) arbitrated. We developed our own risk of bias tool based on the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011), tailored to this review. We developed this tool as data extraction continued. We then discussed risk of bias for all studies to ensure uniformity and agreement. Where possible, we sought study protocols to aid assessment of selective outcome reporting bias.

We assessed each study according to the following domains:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective reporting; and
- any other potential threats to validity.

To assess risk of bias for these domains we looked for: evidence of, for example, use of randomisation tables or lists or randomisation by computer; allocation concealment via, for example, opaque, sealed envelopes or pharmacy assignment; explicit statements on blinding (or otherwise) and clear descriptions of who was blinded (we did not judge blinding of outcome assessment in relation to mortality, as it would not have been affected by the outcome assessor); specific statements regarding an intention-to-treat (ITT) analysis being conducted, statements about dropouts, or data presented in a way that allowed the number of participants included in analyses to be ascertained; all outcomes in protocols being reported in the manuscript; and factors such as poor recruitment rates, differences in baseline demographics, inadequate or poorly defined methods for assessing outcomes such as wound infections and length of hospital stay.

We classified risk of bias as 'high', 'low' or 'unclear' for each of these domains.

Measures of treatment effect

Categorical data are presented as a risk ratio (RR) with 95% confidence interval (CI). We present continuous data as a mean difference (MD) or standardised mean difference (SMD) with 95% CI, as appropriate.

Unit of analysis issues

The unit of analysis in all included studies was the individual participant. No studies used cluster-randomisation.

Dealing with missing data

We contacted the nominated trial investigator for the included studies to obtain any missing data necessary for meta-analysis (NH and SJL). We had planned to calculate missing standard deviations from the standard errors or confidence intervals, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011), but this was not required. Where standard deviations could not be calculated, we planned to impute these using the mean of the reported standard deviations from the other studies, but this was not needed.

Assessment of heterogeneity

We assessed statistical heterogeneity using visual inspection of the forest plot, the I^2 statistic (Handbook 2011), and the Chi^2 test. We considered an I^2 value of greater than 50% along with a P value of less than 0.10 in the Chi^2 test to be indicative of the need to further examine heterogeneity (Handbook 2011).

Assessment of reporting biases

We assessed publication bias and other small study effects in a qualitative manner using a funnel plot.

Data synthesis

We performed analyses in RevMan 5.3 (RevMan 2014). Analyses comprised only within-study comparisons rather than individual-level data. Comparisons were based on an intention-to-treat analysis. We used a random-effects model for the meta-analysis of results, as there was a high level of clinical heterogeneity among the included studies. Three authors (NH, ST and SJL) discussed the results for each outcome measure within each study, to determine the inclusion of data in the meta-analyses.

Where complications were reported as percentage incidence, we converted this into the number of participants who experienced complications. In the case of Snyderman 1999 we estimated the number of wound infections, pneumonias and urinary tract infections per treatment group by visual inspection of 'Figure 2' within their manuscript.
All authors participated in double-checking all of the continuous outcome data entered into RevMan for the included studies.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses as follows (and comparison of subgroups using an interaction term if appropriate).
Subgroup analysis of the participants, according to type of surgery:

- anatomical site of surgery;
- type of reconstruction ('primary closure' versus 'free flap').

Subgroup analysis of the intervention to assess clinical heterogeneity:

- preoperative immunonutrition versus placebo drink;
- postoperative immunonutrition versus postoperative polymeric feed.

Sensitivity analysis

Sensitivity analyses were based on the risk of bias of the studies (i.e. the removal of studies judged at high risk of bias for at least two of the factors assessed), or if they were quasi-randomised trials. We also considered the appropriateness of comparing random-effects and fixed-effect estimates of each outcome variable. If publication bias was suspected we planned to perform a 'trim and fill' sensitivity analysis of the primary outcomes. To assess trial influence we planned to perform sensitivity analyses by sequentially excluding each study. If it was not possible to conduct an analysis in RevMan 5.3, we would have used Stata (Stata 11, StataCorp).

GRADE and 'Summary of findings' table

We used the GRADE approach to rate the overall quality of evidence (Ryan 2016). Two authors (CA and SJL) made the GRADE ratings and any differences were resolved by consensus of all authors. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we applied this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that any estimate of effect obtained is very uncertain.
The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We included a 'Summary of findings' table (Summary of findings for the main comparison), constructed according to the recommendations described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).
We included the following outcomes in the 'Summary of findings' table: length of hospital stay, wound infection, fistula formation, adverse events/tolerance of feeds and postoperative mortality.

RESULTS

Description of studies

See tables of Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The electronic searches retrieved 1434 results. We identified three further records through scanning the reference lists of included studies. After screening titles and abstracts, we discarded 708 duplicates and 699 irrelevant records. We sought full texts for the remaining 29 records and retrieved trial information from ClinicalTrials.gov for one record (NCT03261180).
Upon screening we excluded a further nine records (see Characteristics of excluded studies). One of the records for which we sought a full text was the protocol associated with Palma-Milla 2016; as such, only eight studies are shown in the Characteristics of excluded studies table). One relevant trial is not yet recruiting (NCT03261180).
Nineteen studies (with 20 publications) met the full inclusion criteria. We therefore included 19 unique studies comprising 1099 participants, as shown in Figure 1. The searches were completed in February 2018.

Included studies

We included 19 studies see Characteristics of included studies.
One study was only published as an abstract (Felekis 2005). We obtained additional unpublished data from 12 studies (Casas-Rodera 2008; De Luis 2002; De Luis 2003; De Luis 2004; De Luis 2005; De Luis 2007; De Luis 2009; Falewee 2014; Ghosh 2012; Riso 2000; Sorensen 2009; Turnock 2013).

Design

All of the included studies were randomised trials of an active (immunonutrition) intervention versus control (see Table 1 for a description of the interventions used).

Sample sizes

Total sample sizes ranged from 8 to 209 participants (Table 2). Twelve of the 19 studies had fewer than 25 patients in each treatment group.

Setting

Studies were set in hospitals and conducted in eight countries. Seventeen studies were single-site studies and one study was multicentre (Falewee 2014). We identified eight studies from Spain (Casas-Rodera 2008; De Luis 2002; De Luis 2003; De Luis 2004; De Luis 2005; De Luis 2007; De Luis 2009; De Luis 2014). Two studies were from the USA (Snyderman 1999; Sorensen 2009), two studies from Greece (Felekis 2005; Felekis 2010), and one from each of the following countries: France (Falewee 2014), Italy (Riso 2000), Netherlands (Van Bokhorst 2000/2001), New Zealand (Turnock 2013), Malaysia (Azman 2015), Japan (Hanai 2018), and the UK (Ghosh 2012).

Participants

The 19 studies included in this review represent a total of 1099 participants undergoing head and neck cancer surgery of the upper aerodigestive tract (sites included mouth, pharynx and larynx) (see Characteristics of included studies).

Studies included adults only and the mean age of study participants across studies ranged from 47 to 66 years (Table 2). There were more males than females in most studies, and the mean body mass index (BMI) reported across studies ranged from 22.1 to 26.5 (Table 2). The stage of disease was reported in 18 studies with only one study not reporting this (Felekis 2005; published as an abstract).

Studies excluded people with a range of medical conditions including impaired renal or hepatic function (16 studies), ongoing infections (13 studies) and autoimmune disorders (13 studies), those on steroid treatment (10 studies) or nutritional oral supplementation in the previous six months and those who were malnourished/had severe cancer cachexia or sarcopenia (seven studies), those who were well nourished (two studies) or morbidly obese (one study), patients with contraindications to enteral nutrition/patients with inborn errors of metabolism relating to the composition of the formula (two studies), patients treated with chemotherapy and/or radiation therapy delivered to the head and neck area during the previous year (three studies) or chemoradiotherapy or other treatment protocols concurrent to the intervention (one study), patients testing positive for HIV (three studies), patients with diabetes (five studies), and pregnant or breast-feeding women (four studies).

Interventions

Detailed descriptions of the interventions used in each of the included studies are shown in Table 1. Most studies (16/19) used immunonutrition formulas that contained arginine, one study used glutamine powder, one study used an eicosapentaenoic acid (EPA)-enriched oral nutritional supplement and one used an unspecified product. When study feeds were given pre-operatively, the length of intervention ranged from around 5 to 14 days (n = 9 studies). There was more variation when feeds were given postoperatively, with a range of around 5 days to an average duration of 22 days ± 12 days (n = 19 studies). Most studies (12/19) based the intake of study feeds on body weight or 'requirements', some (n = 5/19) used a set amount (e.g. 1000 mL per day, or 30 g powder per day) and others (n = 2/19) did not state the amount. Follow-up time frames also varied considerably across studies, and ranged from five days post-operation (De Luis 2003) to greater than or equal to 16 months (Van Bokhorst 2000/2001 for survival data).

Immunonutrition was given postoperatively in all studies, and nine studies gave immunonutrition pre-operatively as well as postoperatively (Table 1). One study with three treatment groups gave pre-operative immunonutrition alone in one group (Falewee 2014), but data from that group were not included in analyses. A commercial polymeric feed was used in the control group postoperatively in most studies (17/19), some of which contained additional fibre (Table 1). In six studies the control group received a standard polymeric feed preoperatively as well as postoperatively (Falewee 2014; Felekis 2005; Felekis 2010; Ghosh 2012; Sorensen 2009; Van Bokhorst 2000/2001). In one study, two groups (one of which had received the control feed both pre- and postoperatively and the other only postoperatively) were combined in their analyses (Snyderman 1999).

Outcomes

Of the outcomes considered, mortality was most commonly reported (14 studies; we obtained unpublished data on mortality for eight studies (Casas-Rodera 2008; De Luis 2003; De Luis 2004; De Luis 2005; De Luis 2007; De Luis 2009; Falewee 2014; Sorensen 2009), with the remaining data being available in the paper or abstract), followed by wound infection (12 studies), adverse events/tolerance of feeds (11 studies), length of hospital stay (10 studies) and fistulae (10 studies).

Excluded studies

We excluded eight studies (see Characteristics of excluded studies). We excluded one study (Buijs 2010), which was a follow-up of patients from a study already included in the review (Van Bokhorst

2000/2001). Buijs 2010 reported on long-term survival (≥ 10 years) and we felt that including mortality data from a much longer follow-up time period than all other included studies (which measured mortality in a relatively short period of time post-intervention) would make the results more difficult to interpret.

Three studies were not randomised (De Luis 2013; Linn 1988; Reis 2016), and four had no suitable control group (De Luis 2005a; De Luis 2010; De Luis 2015; Palma-Milla 2016).

Risk of bias in included studies

The risk of bias for each study is described in detail in the Characteristics of included studies table. Details of risk of bias judgements for each study are presented in Figure 2, with an overall summary graph in Figure 3. Allocation concealment methods were most poorly reported, resulting in the greatest number of 'unclear' risk of bias assessments. Details of methodological quality are also presented in Table 3.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

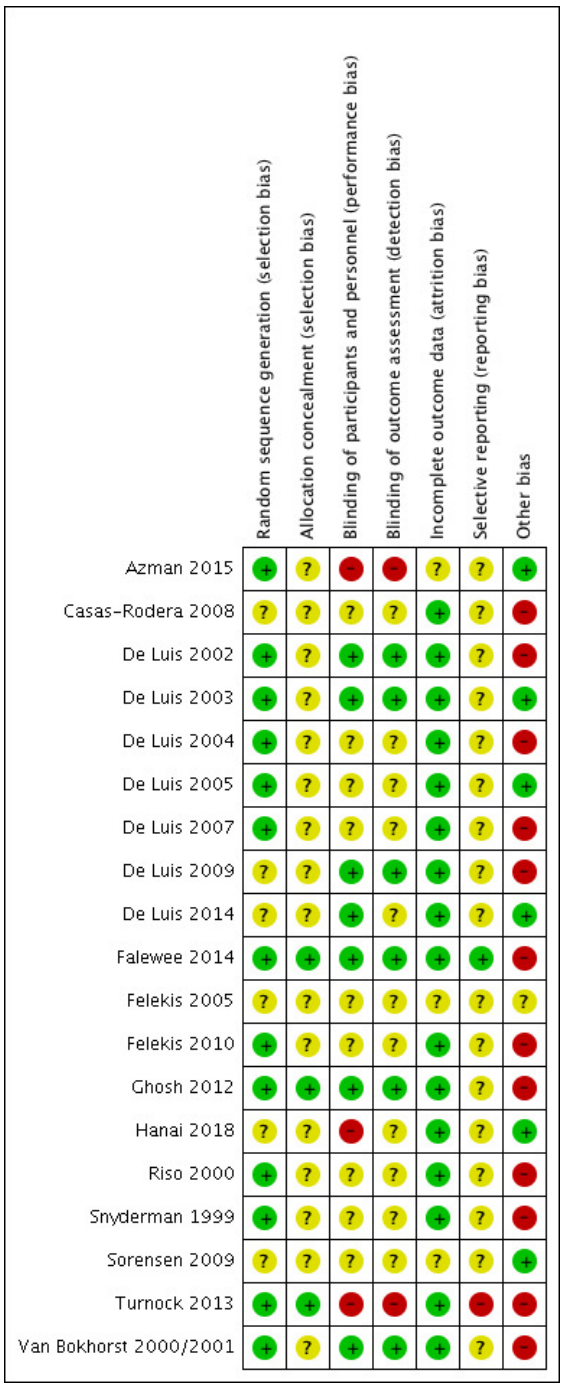
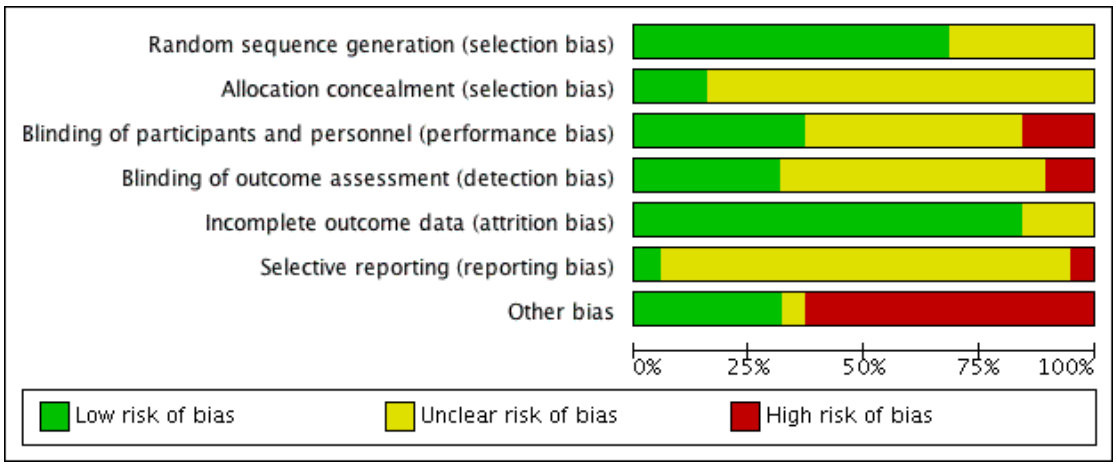


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

We classed 13 studies at low risk of bias due to acceptable randomisation sequence generation through the use of computer-generated randomisation, randomisation lists, tables or a "randomization generator" (Azman 2015; De Luis 2002; De Luis 2003; De Luis 2004; De Luis 2005; De Luis 2007; Falewee 2014; Felekis 2010; Ghosh 2012; Riso 2000; Snyderman 1999; Turnock 2013; Van Bokhorst 2000/2001). In six studies the method of random sequence generation was not clear or not stated and therefore we classed this as an unclear risk of bias (Casas-Rodera 2008; De Luis 2009; De Luis 2014; Felekis 2005; Hanai 2018; Sorensen 2009).

Allocation concealment

We considered 16 studies to be at unclear risk of bias due to inadequately reported methods of allocation concealment. Of these, eight reported the use of envelopes but did not state whether or not they were opaque (Azman 2015; De Luis 2002; De Luis 2003; De Luis 2004; De Luis 2005; De Luis 2007; Riso 2000; Sorensen 2009). We classed the other eight at unclear risk of bias because allocation concealment was either not stated (Casas-Rodera 2008; De Luis 2009; De Luis 2014; Felekis 2005; Hanai 2018; Snyderman 1999; Van Bokhorst 2000/2001), or was not clear as documented (Felekis 2010). We classed three studies as low risk of bias due to the use of central telephone assignment (Falewee 2014; Ghosh 2012), or the use of opaque, sealed envelopes (Turnock 2013).

Blinding

Participants and personnel

Participants can be adequately blinded with this intervention, therefore we judged studies where patients were not blinded to be at high risk of bias. Two studies stated that they were not blinded and we classed them at a high risk of bias (Azman 2015; Turnock 2013), and one study used sachets in the intervention group and no treatment in the control group, so it was assumed to be unblinded and at high risk of bias (Hanai 2018). We classed nine studies at an unclear risk of bias because they either did not state whether or not participants and personnel were blinded (Casas-Rodera 2008; Felekis 2005), or they stated that the study was blinded but did not state who was blinded (De Luis 2004; De Luis 2005; Felekis 2010; Riso 2000), or they described partial blinding (Snyderman 1999; Sorensen 2009). We classed all other studies (seven) as at low risk of bias.

Outcome assessment

Judgements for risk of bias in regards to the blinding of outcome assessment were as described above for blinding of participants and personnel with two exceptions. De Luis 2014 stated that "Blinding of patients and dietitians involved in patient treatment was maintained", but they did not indicate who the outcome assessor was; as such, we judged it at unclear (rather than low) risk of bias. Hanai 2018 did not indicate who the outcome assessor was or whether or not anyone was blinded; as such, we judged it at unclear (rather than high) risk of bias.

Incomplete outcome data

We considered most studies at low risk of bias for incomplete outcome data, with the exception of three studies that we classed at an unclear risk of bias because they did not mention whether or not an intention-to-treat (ITT) analysis had been conducted/ whether any dropouts had occurred, or did not present data in such a way as to be able to determine the number of participants included in analyses (Azman 2015; Felekis 2005; Sorensen 2009). The remaining studies either had no attrition according to the numbers included in tables/figures, or stated that an ITT analysis had been conducted or that there were no dropouts/losses to follow-up. (NB: we obtained additional data for one study to enable an ITT analysis to be conducted; Falewee 2014).

Selective reporting

We classed most studies (17) at an unclear risk of selective reporting bias because protocols were not available to judge whether or not selective reporting had occurred. We classed one study at a low risk of bias because the primary outcome stated in the protocol was reported in the paper (Falewee 2014) (no secondary outcomes were specified in the protocol so it was not possible to judge whether selective reporting of secondary outcomes had occurred). We classed one study at a high risk of bias because not all primary outcomes stated in the protocol were presented in the manuscript (Turnock 2013).

Other potential sources of bias

Five studies reported problems with recruitment (Falewee 2014; Ghosh 2012; Snyderman 1999; Turnock 2013; Van Bokhorst 2000/2001), three reported baseline differences between treatment groups (Ghosh 2012; Snyderman 1999; Van Bokhorst 2000/2001), and six had poorly defined methods for assessment of wound infection (Casas-Rodera 2008; De Luis 2002; De Luis 2004; De Luis 2007; De Luis 2009; Felekis 2010). We classed these studies at high risk of bias for these other potential sources of bias. Of the 10 studies that reported length of hospital stay, six did not describe how this was determined (De Luis 2002; De Luis 2004; De Luis 2007; De Luis 2009; Riso 2000; Turnock 2013). The assessment of tolerance of feeds was not based on consistent descriptions across studies.

One study was available only as an abstract and we judged it at unclear risk of other bias (Felekis 2005). We classed the remaining studies at low risk of bias for other potential sources of bias as there was no evidence for this in the published data (Azman 2015; De Luis 2003; De Luis 2005; De Luis 2014; Sorensen 2009).
Most studies were small, with sample sizes that were unrealistically low for detecting clinical complications.

Effects of interventions

See: **Summary of findings for the main comparison** Immunonutrition compared to standard care for patients undergoing surgery for head and neck cancer

Immunonutrition versus standard care

Primary outcomes

Length of hospital stay

Length of hospital stay was reported in 10 studies. The mean length of stay ranged from 15.3 days to 31.1 days in immunonutrition groups and from 17.4 days to 36.1 days in control groups. We found no evidence of a difference between treatment groups in the length of hospital stay, but the confidence interval around the effect estimate was wide (mean difference -2.5 days, 95% confidence interval (CI) -5.11 to 0.12 (P = 0.06); 10 studies, 757 participants) (GRADE: *low-quality evidence*). The results showed little evidence of heterogeneity between studies (Chi^2 = 12.89, P = 0.17, I^2 = 30%) (Analysis 1.1).

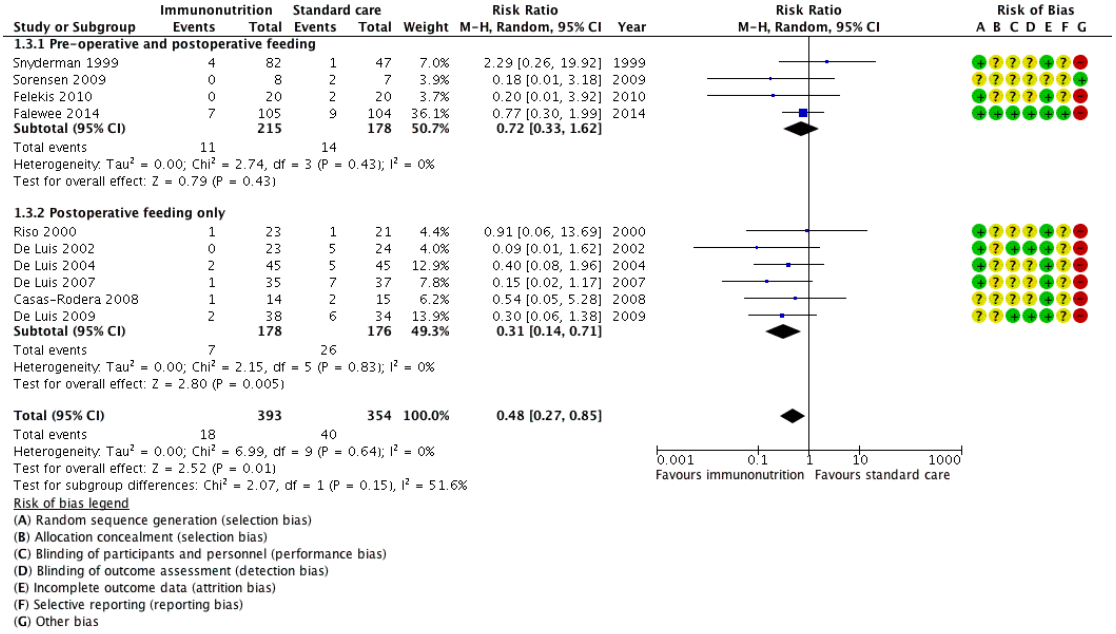
Wound infections

Wound infections were reported in 12 studies, of which 10 studies reported events. One study reported 'wound complications' as the number with Clavien-Dindo grades above 3, above 2 or all grades and was not included in the meta-analysis (Hanai 2018). Absolute risks ranged from 0% (0/45) to 61% (17/28) in the immunonutrition groups and from 0% (0/45) to 59% (17/29) in the control groups. Events were more common (in both treatment groups) in studies that had used pre- and postoperative intervention (a total of 95 events among 458 participants) than in studies that used only postoperative intervention (a total of 14 events among 354 participants). We found no evidence of a difference between treatment groups for this outcome. The combined risk ratio (RR) was 0.94 (95% CI 0.70 to 1.26, P = 0.66; 12 studies, 812 participants) (GRADE: *very low-quality evidence*), with little evidence of heterogeneity between trials (Chi^2 = 4.12, P = 0.90, I^2 = 0%) (Analysis 1.2).

Fistula formation

Fistula formation was reported in 10 studies, all of which reported events. The absolute risk was 5.4% (range 0% (0/23) to 7% (7/105)) in the immunonutrition groups and 11.3% (range 2% (1/47) to 29% (2/7)) in the control groups. There was a reduction in fistula formation with immunonutrition compared to standard care; the combined RR was 0.48 (95% CI 0.27 to 0.85, P = 0.01; 10 studies, 747 participants) (GRADE: *low-quality evidence*), with little evidence of heterogeneity between studies (Chi^2 = 6.99, P = 0.64, I^2 = 10%) (Analysis 1.3; Figure 4).

Figure 4. Forest plot of comparison: 1 Immunonutrition versus standard care, outcome: 1.3 Fistula formation.



Adverse events/tolerance of feeds

Adverse events in relation to aspects of tolerance of feeds were reported in 11 studies, and included intolerance to feed (Snyderman 1999) and gastrointestinal intolerance (Falewee 2014), abdominal distension, abdominal cramps or emesis (Riso 2000), and diarrhoea (Azman 2015; Casas-Rodera 2008; De Luis 2002; De Luis 2004; De Luis 2007; De Luis 2009; Hanai 2018). One study stated that "gastrointestinal tract tolerance of both formula diets was excellent in both groups, and no dropouts occurred because of intolerance" (Felekis 2010); for analysis we assumed that there were zero adverse events in both treatment groups. In two studies, a control feed was not used and adverse events were documented only in relation to withdrawals from the immunonutrition treatment groups (one per study); data from these two studies were not included in the meta-analysis (Azman 2015; Hanai 2018). Among the nine studies that we included in the meta-analysis, absolute risks ranged from 0% (0/20) to 40% (18/45) in the immunonutrition groups and from 0% (0/20) to 29% (6/21) in the control groups. There was no evidence of a difference between treatment groups for this outcome. The combined RR was 1.33 (95% CI 0.86 to 2.06, P = 0.20; 9 studies, 719 participants) (GRADE: *very low-quality evidence*), with little evidence of heterogeneity between

trials (Chi² = 7.11, P = 0.42, I² = 2%) (Analysis 1.4).

Secondary outcomes

All-cause mortality

Mortality was reported in 14 studies (NB: additional unpublished information was obtained from eight authors) and ranged from 0% (0/105) to 14% (4/28) in the immunonutrition groups, and from 0% (0/45) to 8% (2/24) in the control groups. The follow-up timeframes varied considerably across studies, and ranged from 30 days to greater than or equal to 16 months in those studies that were meta-analysed (NB: one study did not state the follow-up timeframe). There was no evidence of a difference between treatment groups for this outcome. The combined RR was 1.33 (95% CI 0.48 to 3.66, P = 0.59; 14 studies, 776 participants) (GRADE: *low-quality evidence*), with little evidence of heterogeneity between studies (Chi² = 3.66, P = 0.45, I² = 0%) (Analysis 1.5).

Postoperative complications

Other clinical complications such as pneumonia and urinary tract infections were uncommonly reported (Table 4), but there was no evidence of a reduction (or an increase) with immunonutrition.

Subgroup analysis

The direction of effect for length of stay, wound infection, fistula formation and mortality did not differ between studies that had given immunonutrition both pre- and postoperatively and studies that had given it only postoperatively (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.5). We observed some differences in effect sizes between the subgroups, but most subgroups included six or fewer studies (with the exception of eight studies in the postoperative feeding only subgroup for mortality) and P values for subgroup differences ranged from 0.08 for length of stay (Analysis 1.1) to 0.77 for mortality (Analysis 1.5) (corresponding I² values were 66.6% and 0%, respectively). Studies that had given immunonutrition only postoperatively showed a more beneficial effect on fistula formation than those that had given immunonutrition pre- and postoperatively (RR 0.31, 95% CI 0.14 to 0.71, P = 0.005, 6 studies, 354 participants, and RR 0.72, 95% CI 0.33 to 1.62, P = 0.43; 4 studies, 393 participants, respectively). There was a difference in the direction of effect for adverse events/tolerance of feeds between studies that had given immunonutrition both pre- and postoperatively and studies that had given it only postoperatively, but such a comparison is not warranted as only two studies were included in the pre- and postoperative feeding analysis.

For wound infections, more events were reported in the six studies that used pre- and postoperative immunonutrition (n = 48 events among 247 participants in the immunonutrition group and n = 47 events among 211 participants in the standard care group) than in the six studies that used only postoperative immunonutrition (n = 5 events among 178 participants in the immunonutrition group and n = 9 events among 176 participants in the standard care group).

Only one study gave pre-operative immunonutrition alone so it was not possible to conduct a subgroup analysis of preoperative immunonutrition versus placebo drink (Falewee 2014).

We did not conduct subgroup analyses according to the type of surgery as data were not presented in such a way in the original publications as to allow this to be done.

Sensitivity analysis

We did not conduct sensitivity analyses in which we removed studies judged at high risk of bias for at least two of the factors assessed or where we removed quasi-randomised trials because no studies met these criteria. We calculated random-effects estimates for each outcome variable due to the extent of clinical heterogeneity. We did not judge fixed-effect estimates to be appropriate.

Publication bias

We examined publication bias for all outcomes by visual inspection of funnel plots and we have presented three of these: length of hospital stay (Figure 5), wound infection (Figure 6) and fistula formation (Figure 7). Study numbers were relatively small for these outcomes, which made it difficult to definitively assess publication bias; however, there was a suggestion of publication bias for length of hospital stay (Figure 5). Given the absence of clear publication bias, however, we did not conduct a trim and fill analysis for the primary outcomes.

Figure 5. Funnel plot of comparison: 1 Immunonutrition versus standard care, outcome: 1.1 Postoperative length of hospital stay [days].

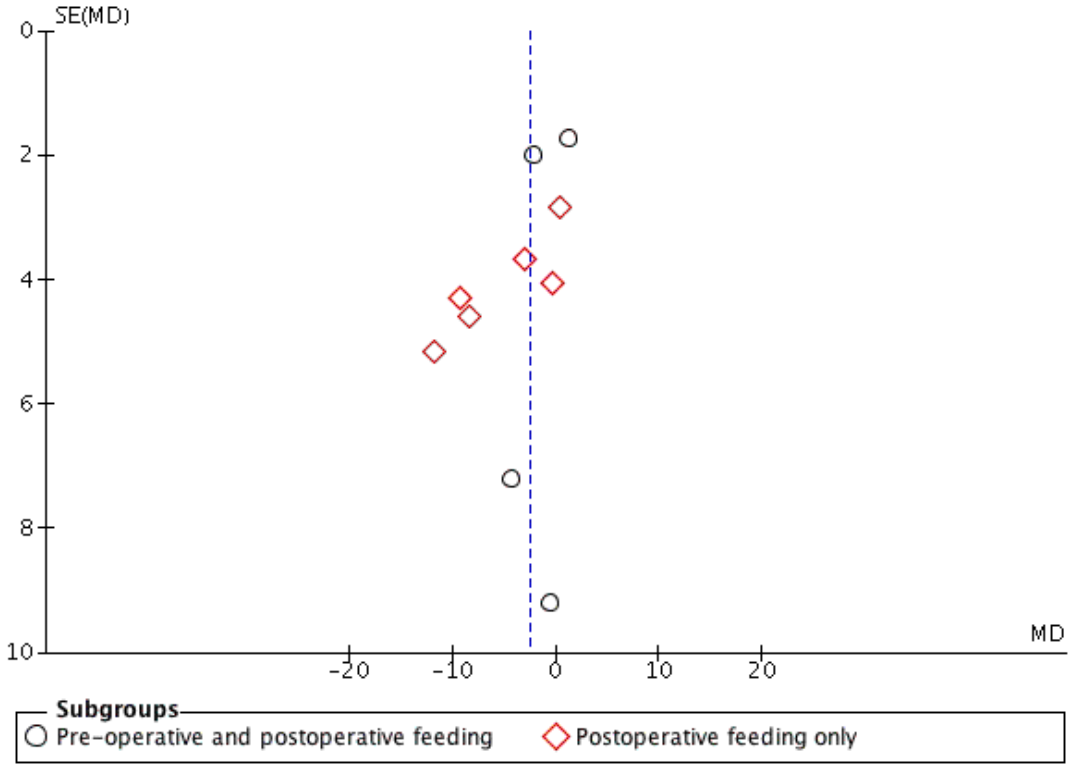


Figure 6. Funnel plot of comparison: 1 Immunonutrition versus standard care, outcome: 1.2 Wound infection.

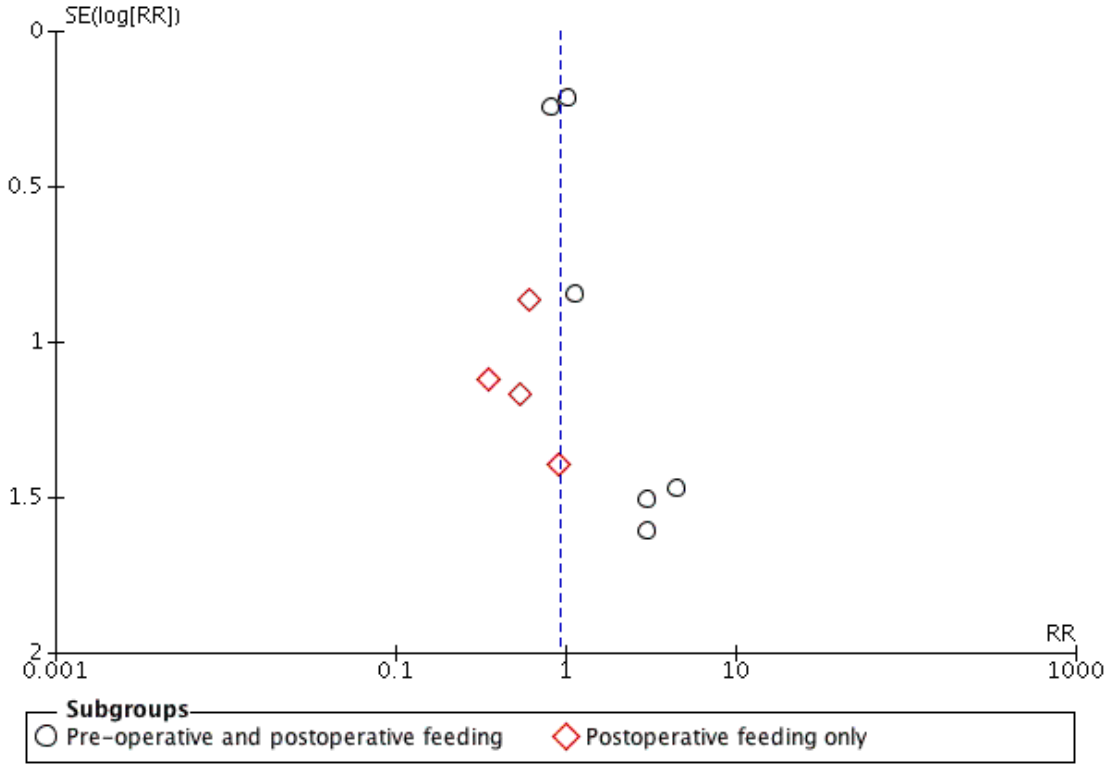
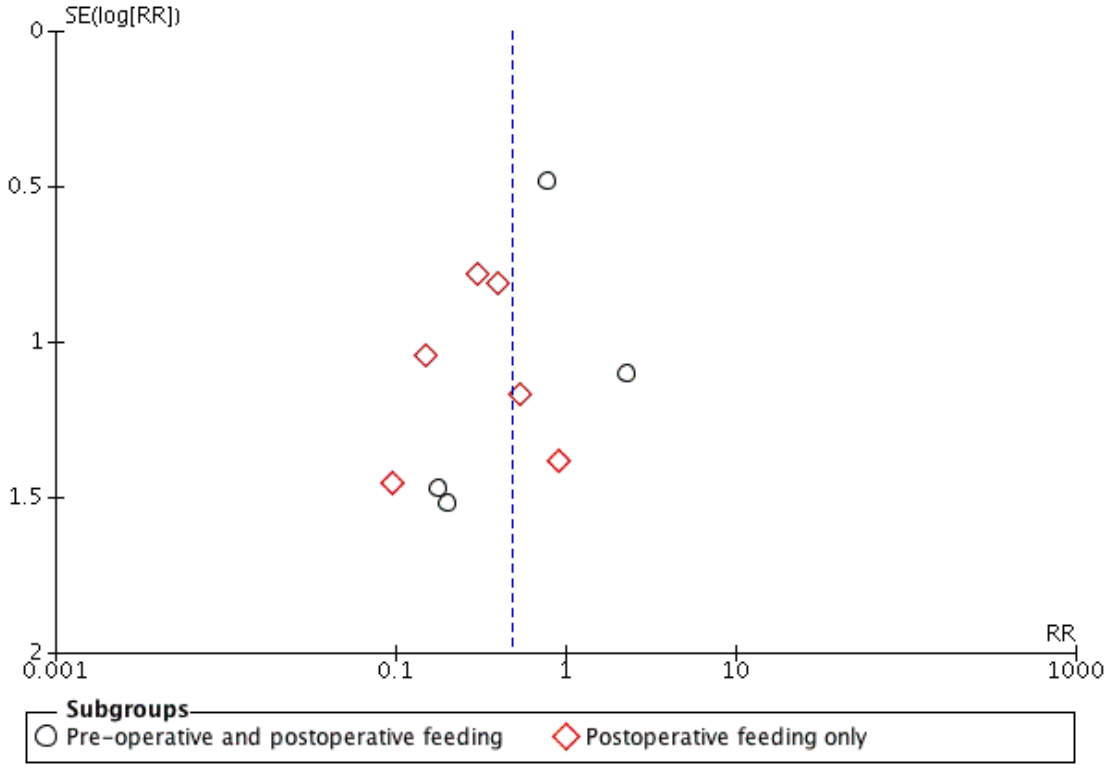


Figure 7. Funnel plot of comparison: 1 Immunonutrition versus standard care, outcome: 1.3 Fistula formation.



DISCUSSION

Summary of main results

Pooled estimates showed no evidence of a difference in the length of hospital stay between treatment groups. The mean difference was -2.5 days but the estimate was imprecise (95% confidence interval (CI) -5.11 to 0.12) and included the null value. There may be an approximate halving of the risk of fistulae formation (risk ratio (RR) 0.48) with immunonutrition, but the evidence was of low quality. Immunonutrition may have little or no effect on wound infection and mortality, and there was little or no difference in adverse events such as diarrhoea between the treatment groups. We did not formally meta-analyse other complications because of their heterogeneity. The findings are summarised in Summary of findings for the main comparison. Length of hospital stay was reduced in 8 of the 10 studies where it was recorded. No reduction in hospital stay was seen in the largest recent study (Falewee 2014). Reduced fistula formation was seen in patients receiving immunonutrition, but no other reductions in clinical complications such as wound infections were seen. No substantial differences in the findings were seen when looking at the timing of intervention (i.e. pre- and postoperative or just postoperative). Where stated, all but two of the studies looking at in-hospital postoperative immunonutrition used arginine as an immunonutrient; Azman 2015 used glutamine and Hanai 2018 used an eicosapentaenoic acid (EPA)-enriched supplement. Ten studies evaluated postoperative nutrition alone and nine studies included pre- and postoperative nutrition. One study provided only preoperative immunonutrition in one of their treatment groups (Falewee 2014), but the numbers of patients and complications were too small to draw any conclusions. Studies that gave immunonutrition only postoperatively showed a larger beneficial effect on fistula formation than studies that gave it both pre- and postoperatively (RR 0.31 versus 0.72, respectively). One study that gave immunonutrition both pre- and postoperatively reported more fistulas with immunonutrition than standard care (Snyderman 1999). The reasons for this are not clear and are in contrast with all other stud-

ies (irrespective of timing of intervention), which reported fewer fistulas with immunonutrition than standard care. The cause of mortality was often poorly reported and it may be inappropriate to ascribe any difference in mortality to immunonutrition. However, no evidence of any effect of immunonutrition on mortality (which was low) was seen. We did not formally analyse potential clinical complications such as pneumonia, diarrhoea, cardiovascular effects and the relationship of nutritional status to outcomes due to either limited data or outcomes not having been recorded. Overall, most studies were too small to provide precise estimates of intervention effects.

Overall completeness and applicability of evidence

Completeness

We attempted to identify and synthesise all existing research to provide a comprehensive estimate of the effect of immunonutrition on postoperative recovery following head and neck cancer surgery. We included 19 studies that recruited 1099 participants. We also conducted the largest systematic review prior to this one, which included 10 randomised controlled trials (RCTs) that had recruited 605 participants (Stableforth 2009). One of the trials (De Luis 2005a), which had been included in our previous review, was not included here as the immunonutrition intervention was administered at the point of discharge. Another systematic review from 2012 included 14 studies with 601 participants (Casas Rodera 2012); three of the studies in that review were not relevant to ours as two studies compared two doses/types of immunonutrients (De Luis 2005a; De Luis 2010), and one study, as noted above, was part of another publication (Buijs 2010). A third systematic review from 2014 included six studies and 397 participants, all of which were included in our review (Vidal-Casariego 2014). Despite being the largest systematic review to date, it is possible that our search strategies may not have identified all of the existing literature.

We looked at similar outcomes to other systematic reviews, but we did not analyse further outcomes reported in studies such as pneumonia, cardiovascular effects and the relationship of nutritional status to outcomes due to limited data.

This review was systematic, using extensive searches of several databases and inclusive search terms. We did not include unpublished literature, but we felt it unlikely that there are large unpublished trials that demonstrate a substantial effect of immunonutritional interventions in head and neck cancer. We made attempts to contact senior or corresponding authors as published in the original papers. We received further data from Dr De Luis, Professor Jones (re: Ghosh 2012), Dr Riso and Dr Falewee regarding research methods and outcomes.

Applicability

Most studies applied exclusion criteria to individuals for study participation. These frequently included renal or hepatic impairment, existing infection and altered immune function. Three studies excluded participants who were well nourished (De Luis 2003; De Luis 2005; Van Bokhorst 2000/2001), one excluded those who were morbidly obese (Snyderman 1999), and seven excluded people who were malnourished (Azman 2015; De Luis 2002; De Luis 2004; De Luis 2007; De Luis 2009; De Luis 2014; Turnock 2013). Studies included in this review were conducted in various countries, incorporating a range of cultures and healthcare systems. Eight were undertaken in Spain (seven of which were conducted by the same group), two in the United States, one in New Zealand, one in Malaysia, one in Japan and the remainder in western Europe. This may have had an effect on outcomes. For example, standard healthcare practice (e.g. discharge policies, implementation of Enhanced Recovery After Surgery (ERAS) protocols, etc.) is likely to vary across countries, thus making comparisons across studies less meaningful. In addition, the studies were reported over an approximate 18-year period during which there are likely to have been changes in clinical practice. However, it was not possible from the information provided to assess the impact of this possibility. There were also differences between studies regarding patient populations and types of surgery. As such, it remains unknown who is most likely to benefit from immunonutrition (if indeed there is a true benefit) based on the included studies.

Quality of the evidence

Assessments of the quality of evidence for each outcome are presented in Summary of findings for the main comparison.

Methodology

In general studies were poorly reported with a large proportion of unclear risk of bias assignments for several of the items assessed (Figure 2; Figure 3). We assigned blinding of outcome assessment an unclear risk of bias in 11 studies and 'other' bias a high risk of bias in 11 studies (examples of 'other' bias included difficulties in recruitment/not meeting target sample size, and evidence of some baseline differences between treatment groups).

The generation of the random allocation sequence was reported in 13 studies (Table 3). In nine studies allocation was concealed using sealed envelopes but it was not stated whether or not these were opaque in eight of the studies (one explicitly stated that opaque envelopes were used). Concealment of allocation was achieved by using a central telephone assignment in two studies. Where stated, all studies were double-blind (as opposed to single-blind), although there was an overall lack of description of how this was achieved. One study (published as an abstract; Felekis 2005) did not state whether an intention-to-treat (ITT) analysis was conducted, and for another study we obtained additional data from the authors to enable an ITT analysis to be conducted (Falewee 2014).

More than half of the studies reported use of sample size or power calculations (Table 3), but of those that did, several did not meet the target sample size. Many other studies included small sample sizes, reducing the power of the study to observe clinically important differences in outcomes.

The GRADE rating of the evidence varied for all of the outcomes assessed, but we classed none as high-quality (Summary of findings for the main comparison). The main reasons for downgrading the evidence were small sample sizes and wide confidence intervals around effect estimates, and poor descriptions of the methods used for assessing outcomes reported within studies.

Outcome assessment

Infection is the clinical outcome of interest in this research area. However, this was poorly defined in most studies. Wound infections were not classified by site or severity in most studies. Systemic infection was also poorly defined. Similarly, persistent postoperative fistula was not defined in most studies. A more precise measure of infection and fistula could improve the quality of the evidence base. Wound infections were considerably more common (in both treatment groups) in studies that used pre- and postoperative supplementation than in studies that used only postoperative supplementation, but the reasons for this are not clear. Four of the six studies that used pre- and postoperative supplementation and that reported wound infections were from the same research group, and it is possible that their definition of wound infection or their length of follow-up meant that fewer wound infections were captured in their studies.

Blinding of participants with this intervention is possible and should be undertaken, as an awareness of treatment allocation may result in participants misreporting outcomes. Length of hospital stay is likely to be influenced by variation in discharge criteria, which may result in differences between studies. This lack of uniformity across centres may introduce variability for some outcomes.

Heterogeneity

We observed little evidence of heterogeneity for each outcome (Chi^2 ranged from 3.66 to 12.89, P = 0.17 to 0.91, and I^2 ranged from 0% to 30%). For length of hospital stay and fistula formation, if heterogeneity existed it would be more likely to indicate variation in size of effect as opposed to direction of effect given that most studies suggested a beneficial effect of immunonutrition on postoperative recovery outcomes. Visual inspection of the forest plots and associated data did not indicate that size of study substantially altered the effect size (although it must be noted that the majority of studies had sample sizes of fewer than 25 participants per treatment group).

Potential biases in the review process

Search strategy

Although we believe that our electronic (February 2018) and handsearching strategies have identified all relevant studies, it is possible that we may have missed some available literature or unpublished material. We stopped handsearching at the end of January 2017. We have read reviews and references of recent publications and in the time period until publication other studies may have been published or made available. These will be incorporated into future updates of this review.

Assumptions about the mechanism of effect

The various components of immunonutrition supplements have been shown in studies done *in vitro* and *in vivo* to produce what are considered beneficial changes in immunological function. However, there is little evidence from clinical trials that these mechanisms result in reduced postoperative complications. In particular there is little evidence of the superiority of any given immunonutrient over another, for any given dose regimen, or for the time periods for which the immunonutrients need to be taken to produce benefit. The small size of most studies and the variety of dosing regimens meant that it was not possible to comment on the relative merits of each type or dose of immunonutrient. Future studies are required to examine these issues.

Assumptions about the meta-analyses and results

We think it unlikely that we have introduced bias through the methods used in the review process. The range of outcome metrics reported across studies was small and did not require conversion to common units for use in this review. We used a random-effects model (due to a high level of clinical heterogeneity among included studies), which may have resulted in smaller studies being granted a larger weighting than necessary, potentially biasing the overall meta-analysed results (Handbook 2011). We identified possible publication bias from visual inspection of the funnel plot for length of hospital stay (see Figure 5). Some of the studies published by De Luis et al have similar starting dates and trial designs (see Table 2), however the baseline data are different and in their 2004 paper they reference their 2002 paper as a different study. In their 2009 paper the patient characteristics (age, sex) and baseline data are different from their 2007 paper. However, we have been unable to obtain a response from the authors to clarify that there is no overlap in participants across studies.

We did not formally assess biochemical changes or immunological changes as secondary outcomes (as per the original protocol) because very few papers commented on such changes, and in each paper the markers chosen were different and assessed at differing

time intervals. Meta-analysis of the few papers was thus not possible. Furthermore, given the expected profound influence of the operative inflammatory response on levels of such markers, their interpretation is not straightforward.

Assumptions about study methodology

Studies were not excluded on the basis of methodological quality, but exclusion of poor-quality studies would tend to move effect estimates towards the null. The major limitations of the review relate to the limitations of the literature, and we made a number of assumptions about the comparability of study methodology. In general, complications (especially wound infection) were poorly defined, and follow-up timeframes differed considerably across studies (Summary of findings for the main comparison). It may be difficult to detect any effects on postoperative outcomes in studies conducted at a late stage of disease. Different interventions may not have an equal effect, or even the same direction of effect, for different cancer sites and stages. We stratified our analysis according to whether or not immunonutrition was given both pre- and postoperatively or only postoperatively, but our analyses did not adjust for differences in the composition or volume of immunonutrition formulas provided, nor did they take into account the length of time for which participants were fed. Few studies reported on compliance with the intervention, but given that the feed was usually administered enterally (at least postoperatively) we assumed good compliance levels. Such diversity across studies may mean that results varied due to one or more of these factors, but we feel that this was unlikely to have greatly affected our findings. Of note, seven studies came from one centre, all of which had relatively small sample sizes (total sample sizes in these seven trials ranged from 29 to 90 participants). A number of factors that we were unable to control for also may have affected outcomes, such as the experience of the surgeon, the length of the operation and the success of the operation.

Agreements and disagreements with other studies or reviews

Other reviews have been published on this topic, with similarly positive results (Casas Rodera 2012; Stableforth 2009; Vidal-Casariego 2014). The most recent systematic review and meta-analysis included six head and neck cancer surgery studies (Vidal-Casariego 2014). Compared to that review, we observed a lower reduction in length of hospital stay (2.5 days in our analysis versus 6.8 days in theirs). As done here, the authors of that review also conducted analyses based on the timing of administration of immunonutrition. In contrast with that review, however, we did not meta-analyse infections other than wound infections due to the diverse range reported in studies. Our finding of little difference between treatments in wound infections is similar, as is the reduction in fistula formation with immunonutrition (Vidal-Casariego 2014).

No prior review considered complications directly related to the immunonutrition intervention, and none were found in this review.

Some studies have reported on the tolerability of immunonutrition, but few in detail. In their systematic review, Vidal-Casariego et al reported no increase in diarrhoea, although this was based on very few studies (Vidal-Casariego 2014). Our review suggests that immunonutrition is generally as well tolerated as standard supplements in the head and neck cancer surgery patient group, but this finding is also based on very few studies.

Cost has not been reported in systematic reviews and nor were we able to assess costs due to a lack of published data. Snyderman 1999 considered costs in their study and suggested that a reduction in the infection rate between treatment groups (rates were reported as 23% and 45% in the immunonutrition and standard therapy groups, respectively) could reduce costs given the difference in length of hospital stay between those with and without infectious complications.

Overall, our findings are in agreement with other reviews in head and neck cancer surgery (Casas Rodera 2012; Stableforth 2009; Vidal-Casariego 2014), as well as reviews in gastrointestinal surgery (Marimuthu 2012; Zhang 2012), and suggest a potential benefit of immunonutrition. However, in agreement with Vidal-Casariego 2014, the findings for head and neck cancer are based on poor-quality evidence.

There were insufficient data to exclude substantial effects of immunonutrition on other clinical outcomes or biochemical and immunological parameters.

AUTHORS' CONCLUSIONS

Implications for practice

Fistula formation was reduced by around 50% but there was no reduction in length of stay or wound infections and no effect on mortality. However, our GRADE rating of the evidence quality ranged from low to very low, primarily due to small sample sizes and wide confidence intervals around effect estimates, and poor reporting of methods used to assess outcomes. As such, we cannot be certain about the results, but if the effects on fistulas are real this would represent a clinically useful effect. There was no evidence of detriment from immunonutrition.

The actual volume of feeds taken in these studies was not always explicitly stated and it is possible that a minimum amount of immunonutrition may be needed to achieve clinical benefit. In trials conducted among patients undergoing surgery in other anatomical sites where feeding volumes were low, it was suggested that immunonutrition may be no better than an isonitrogenous control

feed (McCowen 2003). It was also suggested that aggressive enteral feeding improves outcomes from immunonutrition and that pre-operative immunonutrition in surgical patients with cancer might be particularly beneficial (McCowen 2003). In our systematic review, seven studies excluded patients who were malnourished. Given that many patients with head and neck cancer are malnourished, the implications for practice in regard to the findings of this review in such populations remain unknown.

We were unable to relate disease severity to the effect of immunonutrition. For example, severe sepsis may not be responsive to any nutritional intervention, whereas mild illness may improve irrespective of feeding. If future trials can consider these vital points, Level 1 recommendations in favour of immunonutrition might be justified, although presently such evidence is lacking for most clinical indications.

The relatively recent implementation of Enhanced Recovery After Surgery (ERAS) programmes within some healthcare systems may complicate the assessment of specific interventions such as immunonutrition. Enhanced recovery programmes are made up of a composite of around 20 potentially effective interventions covering the preoperative, intraoperative and postoperative periods. Interventions include factors such as the use of minimally invasive surgical procedures, optimal pain relief, early postoperative feeding and early postoperative mobilisation. It could be expected that more interventions might have greater effect, but a recent meta-analysis of enhanced recovery programmes in surgery found that programmes with more elements were no more successful than those with fewer elements (Nicholson 2014). For example, studies with four to seven elements seemed to work as well as those with 11 or more. The difficulty in future studies will be to establish the contribution of individual interventions such as perioperative feeding and the specific effect of immunonutrition compared with standard feeding, when in reality there may be many effective interventions being combined. Of note, the length of hospital stay in our included studies was generally long compared with current practice (Coyle 2016), suggesting that future studies of immunonutrition may have less 'room for improvement' in outcomes such as length of hospital stay, possibly due to the use of ERAS programmes.

Some clinical guidelines recommend the use of immunonutrition in specific populations. For example, immunonutrition has been recommended in elective surgery patients prior to surgery, and postoperatively in 'high-risk' patients (McClave 2013). Others suggest that it may benefit patients undergoing major cancer surgery (including head and neck and gastrointestinal) and severe trauma patients, with recommendations to feed five to seven days prior to and five to seven days after 'uncomplicated' surgery (Weimann 2006). It has also been recommended in some intensive care patients (e.g. upper gastrointestinal surgery patients and patients with mild, but not severe, sepsis) (Kreymann 2006). However, the evidence base in head and neck cancer surgery remains relatively weak and the GRADE rating of evidence was low for all of the outcomes assessed. Nonetheless, given that a relatively recent meta-analysis showed that postoperative infectious complications adversely affect long-term survival (Pucher 2014), any reduction in such complications with immunonutrition might ultimately benefit long-term health.

Implications for research

Systematic reviews and meta-analyses in some surgical populations (e.g. gastrointestinal) are suggestive of a benefit of immunonutrition on length of hospital stay and complications (Cerantola 2011; Osland 2014; Zhang 2012), but the evidence is less convincing for head and neck cancer surgery, primarily due to a lack of large, high-quality trials. In addition, the potential for immunonutrition to improve outcomes of surgery in the ERAS era remain largely unknown. As such, recommendations for its use in head and neck cancer surgery may be premature. Furthermore, and as noted above, the applicability of the findings to malnourished populations (such as those undergoing surgery for head and neck cancer) is questionable, and this systematic review highlights the need for further research on the potential effect of immunonutrition in such populations. There is a clear case for a suitably powered, large contemporary trial to definitively establish the case for using immunonutrition in patients undergoing surgery for head and neck cancer. Some of the key factors to consider when designing such a trial include: an adequate (and achievable) sample size to address the primary outcome(s) (a feasibility or pilot trial may be advisable given the issues with recruitment reported in some trials); an assessment of the extent of malnutrition in the patient population (with appropriate stratification if warranted); collection of detailed information on the volume of immunonutrition study participants actually receive (with a view to assessing whether a minimum amount is required to be effective) and whether or not individual nutritional requirements are met; blinding of participants and personnel where possible; blinding of outcome assessment; and clear definitions of all outcome measures, particularly in regard to local or systemic infection.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by year of study]*

Snyderman 1999

Methods	**Design:** double-blind, parallel-group randomised controlled trial with ≥ 5 days pre- and ≥ 7 days postoperative duration of treatment and 1 month duration of follow-up post-operation
Participants	**Setting:** University of Pittsburgh Medical Center and the University of Louisville, Kentucky; from 1994 to 1996 **Sample size:** 141 • **Number randomised:** 136 • **Number completed:** 129 **Participant (baseline) characteristics:** • **Age:** Impact group mean age = 63 (SD 9.8) years; standard group mean age = 61 (SD 11.7) years • **Gender:** male:female ratio Impact group = 3.3:1; standard group = 2.1:1 • **Baseline differences/other characteristics:** Quote: "The composition of treatment groups was similar. There were no significant differences in patient or tumor characteristics". No significant differences in preoperative weight, weight loss or biochemical measures of nutritional status. Quote: "More patients in the Impact group were randomly assigned to receive preoperative nutritional support (P = .002)." **Inclusion criteria:** Quote: "patients with stage II-IV squamous cell carcinoma of the oral cavity, pharynx, or larynx undergoing oncologic surgery with curative intent and requiring postoperative nutritional supplementation" **Exclusion criteria:** Quote: "malabsorption, immune disorders or immunosuppressive medications, active infection, and morbid obesity (>130% ideal body weight)."
Interventions	**4 arms:** Group I = pre- and postoperative Impact Group II = postoperative Impact Group III = pre- and postoperative standard formula Group IV = postoperative standard formula **Intervention group:** Groups I and II combined as 'Impact' (n = 82) **Comparator group:** Groups III and IV combined as 'standard' (n = 47) Quote: "Standard enteral formulas included Replete, Resource, Isosource, Jevity, Vivonex, and Osmolite. Replete was used in the majority (78%) of control patients." Quote: "Treatment goals consisted of preoperative consumption of a minimum of 500 mL of supplement per day for at least 5 days in treatment groups I and III, and postoperative consumption of an average of 1000 mL per day for at least 7 days in all treatment groups." **Use of additional interventions:** Quote: "All the patients received standard antibiotic prophylaxis, consisting of 24 to 48 hours of intravenous antibiotics. In most cases, a regimen of clindamycin (900mg IV every 8 h) was employed. Continuation of antibiotics for more than 48 hours was only used for the treatment of documented infections."

Snyderman 1999 (*Continued*)

Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "Outcome measures included changes in weight, laboratory evaluations of nutritional status, tolerance of tube feedings, infectious and wound healing complications, and duration of hospitalisation." Results presented for: intolerance, postoperative weight, total protein, albumin, transferrin, haemoglobin, TLC, postoperative infection (total number and site specific percentages), wound healing problem, fistula, hospital days, ICU days. Also amino acid and fatty acids, and cost analysis
Funding sources	Quote: "This study was supported by Novartis Nutrition (formerly Sandoz Nutrition), St Louis Park, Minnesota"
Declarations of interest	None stated
Notes	**Participants lost to follow-up:** Quote: "An intent-to-treat analysis was performed on the entire group (129 patients)." **Recruitment:** Quote: "Because of problems with recruitment into the preoperative arms of the study (groups I and III), patients in the latter part of the study were only randomly assigned to groups II and IV, thus accounting for differences in sizes of treatment groups. " **Stratification:** Quote: "After meeting entry criteria, patients were stratified for site (larynx vs. other), stage (T1-3 versus T4, N0 versus N1 to 3), and preoperative weight loss (0-10 lbs, 11-20 lbs, > 20 lbs)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation tables
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Partial blinding described Quote: "Novartis Nutrition provided Impact and Replete (oral and enteral formulas) in unlabeled containers for patients in groups I and III" and "Patients, physicians, and nurses were blinded to the type of formula used." However, whether blinding was achieved for groups II and IV is not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Partial blinding described Quote: "Novartis Nutrition provided Impact and Replete (oral and enteral formulas) in unlabeled containers for patients in groups I and III" and "Patients, physicians,

Snyderman 1999 (*Continued*)

		and nurses were blinded to the type of formula used." However, whether blinding was achieved for groups II and IV is not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data Quote: "An intent-to-treat analysis was performed on the entire group (129 patients)." Note: 136 patients were randomised and it was stated that "7 patients did not receive any therapy and were withdrawn from the study preoperatively. Reasons for withdrawal included patient noncompliance and medical or laboratory evidence of ineligibility." This equates to ~5% withdrawal. A 'per-protocol' analysis was also conducted and reported
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Quote: "Because of problems with recruitment into the preoperative arms of the study (groups I and III), patients in the latter part of the study were only randomly assigned to groups II and IV, thus accounting for differences in sizes of treatment groups. " However, they do not indicate how many were in each of the 4 groups (they only provide totals for the combined groups), but state that "More patients in the Impact group were randomly assigned to receive preoperative nutritional support (P = .002) ."

Van Bokhorst 2000/2001

Methods	**Design:** double-blind, parallel-group randomised controlled trial with 7 to 10 days pre- and ≥ 10 days postoperative duration of treatment and 7 days duration of follow-up (greater than or equal to 16 months of follow-up for survival)
Participants	**Setting:** Department of Otolaryngology - Head and Neck Surgery of the University Hospital Vrije Universiteit, Amsterdam; from 1 January 1994 through 31 December 1997 **Sample size:** • **Number randomised:** 56 • **Number completed:** 49 **Participant (baseline) characteristics:** • **Age:** Group 1 = 55 ± 10; Group 2 = 60 ± 8; Group 3 = 59 ± 12

	• **Gender:** Group 1 = 11 males, 6 females; Group 2 = 7 males, 8 females; Group 3 = 12 males, 5 females; overall total = 30 males, 19 females • **Baseline differences/other characteristics:** no difference between groups in age, tumour stage, tumour location, comorbidity, weight loss, the ratio between combined mandibular resections and total laryngectomies and the type of reconstructive surgery, mean duration of surgery, mean blood loss. Preoperatively, groups 2 and 3 reached 110% and 113% of their estimated energy requirements, but patients in group 1 reached 79% (P = 0.007). Baseline weight was lower in group 2 than in the other groups; baseline serum albumin differed between groups; baseline numbers of lymphocytes and T lymphocytes ($CD3^+$) and the percentage of T suppressor lymphocytes ($CD8^+$). **Inclusion criteria:** Quote: "Severely malnourished (preoperative weight loss > 10% of body weight over the previous 6 mo) head and neck cancer patients eligible for surgery". Quote: "All patients had a histologically proven squamous cell carcinoma of the oral cavity, larynx, oropharynx, or hypopharynx' **Exclusion criteria:** Quote: "Patients were excluded from the study if they were well nourished (weight loss <10% of body weight); received other investigational drugs or steroids; had renal insufficiency, hepatic failure, or any genetic immune disorder; or had a confirmed diagnosis of AIDS."
Interventions	**3 arms:** Quote: "After stratification for type of surgery (combined mandibular resection or total laryngectomy) and previous radiotherapy (yes or no) the patients were randomly assigned to 1 of 3 treatment groups." Group 1 = no pre-operative and standard postoperative tube feeding Group 2 = standard pre-operative and postoperative tube feeding (NB: this group used as the comparator in this review) Group 3 = arginine supplemented pre-operative and postoperative tube feeding Quote: "Group 1 received no preoperative nutritional support, group 2 received pre-operative enteral nutrition with a specially formulated product that closely reflected the current standard of practice (standard formula), and group 3 received preoperative enteral nutrition in which 41% of the casein was replaced by arginine. Nutritional solutions were isoenergetic and isonitrogenous." Standard formula: 62.5 g protein/L, 6.3 g glutamine/L, 9.8 g nitrogen/L, 48.61 g fat/L, 140.63 g carbohydrate/L, 5250 kJ/L Arginine supplemented formula: 36.85 g protein/L, 12.5 g free arginine/L, 3.7 g glutamine/L, 9.8 g nitrogen/L, 48.61 g fat/L, 153.77 carbohydrate/L, 5250 kJ/L Quote: "Patients in groups 2 and 3 were given enteral nutrition at home for 7-10 d preoperatively through a nasogastric feeding tube" Quote: "Patients in group 1 were stimulated to continue their usual oral diet preoperatively" Quote: "Postoperatively, all patients received tube feeding (1.5 x BEE) starting on the first postoperative day until and X-ray conducted to assess swallowing ability performed 10 d after surgery showed no leakage from anastomoses" **Intervention group:** Group 3: arginine supplemented pre-operative and postoperative tube feeding (n = 17) **Comparator group:** Group 2: standard pre-operative and postoperative tube feeding (n = 15) (Data from group 1, n = 17, not used in this review)

	Use of additional interventions: none stated
Outcomes	**Primary and secondary outcomes:** Primary and secondary outcomes not separated out Van Bokhorst 2000: quality of life assessed via 2 questionnaires: the disease-specific EORTC QLQ-C30 and the generic COOP-WONCA. Time points assessed were recruitment (baseline), day before surgery, day of discharge, 6 months post surgery Van Bokhorst 2001: anthropometric measures included body weight, body composition (BIA), upper midarm circumference, skinfold thickness and muscle function (hand grip strength). Biochemical assessment included serum albumin and electrolytes and liver and kidney function tests Immune variables included: absolute numbers of leukocytes and lymphocytes, total lymphocyte count, percentages of monocytes (CD14+), pan T lymphocytes (CD3+) , T helper lymphocytes (CD4+), T suppressor lymphocytes (CD8+), B lymphocytes (CD19+), natural killer (NK) cells (CD16/CD56+/CD3) and NK-like T cells (CD16/CD56+/CD3+). Also measured human leukocyte antigen-DR (HLA-DR) expression in CD14+ cells, interleukin 6 (IL-6) and tumour necrosis factor (TNF) Clinical outcomes included perioperative use of blood, blood products and antibiotics; the occurrence of postoperative complications; the date of normal swallowing as confirmed by X-ray and the date of discharge from the hospital. Postoperative complications were categorised as absent, minor (including minor wound infections, redness and induration of the wound, pulmonary infections and urinary tract infections) or major (including wound infections requiring surgical drainage, orocutaneous or pharyngocutaneous fistula, flap failure, radiologic signs of anastomotic leakage, respiratory insufficiency, cardiac failure and septic shock) Survival (and cause of death where applicable) were assessed after a follow-up period of $\geq$ 16 months Time points assessed: Quote: "at recruitment into the study, 1 d preoperatively, 1 d postoperatively, 4 d postoperatively, 7 d postoperatively, and on the day of discharge. Follow-up time for survival was $\geq$ 16 mo."
Funding sources	None stated
Declarations of interest	None stated
Notes	**Participants lost to follow-up:** Van Bokhorst 2001 stated "No patient was lost to follow up" in regards to the survival analysis (page 325) **Sample size:** Quote: "To reduce the percentage of major postoperative complications from 60% to 30% in the nutrition intervention groups, the sample size was calculated to be 39 patients per study group with 80% power and 5% significance. Because patient recruitment was much slower than expected, however, recruitment ended on 31 December 1997 for financial reasons." Further publication included data on longer-term follow-up: Buijs N, van Bokhorst-de van der Schueren MA, Langius JA, Leemans CR, Kuik DJ, Vermeulen MA, et al. Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival. *American Journal of Clinical Nutrition* 2010;92 (5):1151-6
Risk of bias	

Van Bokhorst 2000/2001 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned "according to a computer-generated randomization schedule with an equal probability of assignment to any of the nutritional regimens." (Van Bokhorst 2001, page 324)
Allocation concealment (selection bias)	Unclear risk	No statement as to how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding of patients, health care professionals involved in patient treatment and assessors was only possible in groups II and III" (Van Bokhorst 2000, page 438) - these 2 groups were used in analyses
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinding of patients, health care professionals involved in patient treatment and assessors was only possible in groups II and III" (Van Bokhorst 2000, page 438) - these 2 groups were used in analyses
Incomplete outcome data (attrition bias) All outcomes	Low risk	49 patients recruited Quote: (Van Bokhorst 2001) "No patient was lost to follow up" in regards to the survival analysis (page 325) No evidence of attrition bias from published data (figures and tables present data on relevant outcomes for 49 patients)
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Some evidence of baseline differences Sample size not achieved Quote: "Because patient recruitment was much slower than expected, however, recruitment ended on 31 December 1997 for financial reasons."

Riso 2000

Methods	**Design:** double-blind, parallel-group randomised controlled trial with ≥ 10 days (following total laryngectomy) or ≥ 21 days (following partial laryngectomy) duration of treatment and follow-up to hospital discharge

Participants	**Setting:** not stated but authors affiliated to Maggiore della Carita Hospital, Novara, Italy. Stated that the trial was "carried out from January to December 1998" **Sample size:** • **Number randomised:** 44 • **Number completed:** 44 **Participant (baseline) characteristics:** • **Age:** enriched group mean age 60.8 (± 9.1); control group mean age 63.2 (± 5.7) • **Gender:** male/female: enriched 21/2; control 18/3 • **Baseline differences/other characteristics:** Quote: "Characteristics of the patients on enrolment were similar for the two groups" **Inclusion criteria:** Quote: "adult patients with oral, pharyngeal and laryngeal cancer were enrolled." **Exclusion criteria:** Quote: "Exclusion criteria included severely impaired renal function (serum creatinine concentration > 2.5 mg/dl) and hepatic function (total serum bilirubin concentration > 3 mg/dl), autoimmune disorders, insulin-dependent diabetes mellitus, ongoing infections."
Interventions	**Intervention group:** Enteral diet supplemented with arginine (enriched group) (n = 23) **Comparator group:** Isocaloric, isonitrogenous enteral formula (control group) (n = 21) Quote: "At surgery, patients were randomly allocated to two groups: a) patients receiving an enteral diet supplemented with arginine (Nutrison Intensive, Nutricia, Zoetermeer, The Netherlands) (enriched group); b) patients receiving an isocaloric, isonitrogenous enteral formula (Nutrison Protein Plus, Nutricia, Zoetermeer,The Netherlands) (control group)." Quote: "Enteral feeding was started within 24 hrs of surgery at a rate of 40 ml/hour. The infusion rate was progressively increased by 20 ml/hour every 24 hrs until the daily nutritional goal (31.0 total kcal/kg; 25.0 non-protein kcal/kg; 1.5 g protein/kg) was reached, on postoperative day (POD) 4. In the first 3 PODs, all patients received calories and nitrogen by parenteral route to achieve the nutritional goal." **Use of additional interventions:** Quote: "In the first 3 PODs, all patients received calories and nitrogen by parenteral route to achieve the nutritional goal." Quote: "Prophylactic antibiotic treatment (amoxicillin/clavulanate, 2.2 g bid i.v.) was given for 7 days postoperatively."
Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "Preoperatively and on postoperative days 1, 4 and 8 the following parameters were evaluated: serum level of albumin (g/dl), prealbumin (mg/dl), and transferrin (mg/dl), total number of lymphocytes (10^6/ml), lymphocyte subsets (CD3, CD4, CD8 and CD4/CD8 ratio; %), and serum immunoglobulin concentrations (IgG, IgA, IgM; mg/dl)." Quote: "All patients were followed-up until discharge. Postoperative complications were recorded as none, minor (urinary tract infection; respiratory tract infection: abnormal chest X-ray), and major (fistula; wound infection: spontaneous or surgical purulent drainage and necrosis; anastomotic leakage). The clinical complications were not defined. Gastrointestinal problems related to enteral feeding were also recorded."

Riso 2000 (*Continued*)

	Abstract states that length of hospital stay was also recorded	
Funding sources	None stated	
Declarations of interest	None stated	
Notes	**Participants lost to follow-up:** no attrition according to figures on outcomes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated (information from authors)
Allocation concealment (selection bias)	Unclear risk	Quote: "Concealed (envelopes)" (information from authors) but not known if these were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blindly performed" (information from authors) but no indication of who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blindly performed" (information from authors) but no indication of who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition according to number of participants included in figures on outcomes
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Subgroup analysis performed on 'malnourished' subset of patients (Quote: "Patients with a weight loss of 10% or more in less than 6 months, with respect to pre-illness body weight"). Unclear if this was a pre-planned analysis; 6 patients in the enriched diet group and 7 in the control group were classed as malnourished
Other bias	High risk	No description of how length of stay was determined. No sample size calculations

De Luis 2002

Methods	**Design:** double-blind, parallel-group randomised controlled trial with an average duration of treatment of 22 days (± 12 days) and duration of follow-up of 14 days postoperatively, or 3 months post-discharge for mortality
Participants	**Setting:** author affiliations in Spain (Institute of Endocrinology and Nutrition, Medicine School and Hospital Rio Hortega, Spain; and Hospital Clinico, University of Valladolid, Valladolid, Spain) **Sample size:** • **Number randomised:** 47 • **Number completed:** 47 **Participant (baseline) characteristics:** • **Age:** mean age was 61.4 ± 11.7 years (63.15 ± 12.7 in group 1 and 59.3 ± 10.5 in group 2) • **Gender:** 5 females, 42 males • **Baseline differences/other characteristics:** Quote: "Characteristics of the patients on enrollment were similar for the two groups." **Inclusion criteria:** oral and laryngeal cancer **Exclusion criteria:** Quote: "severely impaired hepatic function (total bilirubin concentration > 3.5 mg/dl) and renal function (serum creatinine concentration > 2.5 mg/dl) ; ongoing infections; autoimmune disorders; steroid treatment; nutritional oral supplementation in the previous 6 months; and severe malnourishment (weight loss > 10% of body weight)."
Interventions	**Intervention group:** Enteral diet supplemented with arginine and fibre (n = 23) **Comparator group:** Isocaloric, isonitrogenous enteral formula (n = 24) Enteral feeding was started within 24 hours of surgery **Use of additional interventions:** Quote: "Prophylactic antibiotic treatment was given for 7 days postoperatively (ceftazidime, 500 mg three times daily i.v. and clyndamicine 300 mg three times daily i.v.)"
Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "Perioperatively and on postoperative days 7 and 14 the following parameters were evaluated: serum values of prealbumin (mg/dl), transferrin (mg/dl), albumin (g/dl) and total number of lymphocytes (10^6/ml). Postoperative complications were recorded as none, general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive unfiltration, temperature above 38.5°C and isolation of pathogens from the sputum or blood culture and/or urinary tract infection was diagnosed if the urine culture showed at least 105 colonies of a pathogen) and local complications such as fistula and/or wound infection, assessing all complications using standard methods and the same investigator. Gastrointestinal problems related to enteral feeding were also recorded (diarrhoea, > 5 liquid stools in a 24 h period or an estimated volume > 2000 ml/day). Mortality was assessed 3 months after hospital discharge."
Funding sources	None stated

De Luis 2002 (*Continued*)

Declarations of interest	None stated
Notes	**Participants lost to follow-up:** stated that an ITT analysis was conducted Quote: "Sample size was calculated to decrease fistula complication by 20% with 80% power and 5% significance."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No statement in manuscript on the generation of random sequence. Author contacted: tables of random numbers used
Allocation concealment (selection bias)	Unclear risk	No statement in manuscript as to how allocation was concealed. Author contacted: sealed envelopes used (but not known if these were opaque)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The main investigator and patients remained blind to the treatment group."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The main investigator and patients remained blind to the treatment group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data. Quote: "Any drop-outs were present in the study"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Assessment of wound infection poorly described (Quote: "using standard methods by the same investigator") and no description of how length of stay was determined

De Luis 2003

Methods	**Design:** double-blind, parallel-group randomised controlled trial with an average duration of treatment of 20 days (in the supplemented group) and a 5-day duration of follow-up
Participants	**Setting:** author affiliations: Valladolid, Spain **Sample size:** • **Number randomised:** 36

	• **Number completed:** 36 **Participant (baseline) characteristics:** • **Age:** mean age was 59.6 ± 10.9 years (63.1 ± 12.7 years in group 1 and 59.3 ± 10.5 years in group 2) • **Gender:** 2 females, 34 males • **Baseline differences/other characteristics:** Quote: "Characteristics of the patients on enrollment were similar for the two groups" **Inclusion criteria:** a previous weight loss of 5% to 10% (6 months) and oral or laryngeal cancer **Exclusion criteria:** Quote: "Exclusion criteria included severely impaired hepatic function (total bilirubin concentration > 3.5 mg/dl) and renal function (serum creatinine concentration > 2.5 mg/dl), ongoing infections, autoimmune disorders, steroids treatment and well-nourished (weight loss < 10% of body weight)."
Interventions	**Intervention group:** Enteral diet supplemented with arginine (n = 18) **Comparator group:** Isoenergetic, isonitrogenous enteral formula (n = 18) Quote: "Enteral feeding was started within 24 h of surgery" Quote: "Group I received a daily dose of arginine of 12.5 g during an average of 20 days" **Use of additional interventions:** Quote: "Prophylactic antibiotic treatment was given for 3 days postoperatively (ceftazidime, 500 mg three times daily i.v. and clyndamicine 300 mg three times daily i.v.)"
Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out Perioperatively and on postoperative day 5 the following parameters were evaluated: serum values of prealbumin, transferrin, albumin, total number of lymphocytes, interleukin 6, tumour necrosis factor-α and C-reactive protein
Funding sources	None stated
Declarations of interest	None stated
Notes	**Participants lost to follow-up:** stated that an ITT analysis was conducted. No postoperative deaths (information from authors)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Author contacted: tables of random numbers used
Allocation concealment (selection bias)	Unclear risk	Quote: "At surgery patients were randomly allocated (sealed envelopes) to two groups". Also states that the study was a "prospective concealed randomized trial" but no information available on how allocation was

De Luis 2003 (*Continued*)

		concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was blinded (patients and investigator)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study was blinded (patients and investigator)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data Quote: "all randomized patients were included in the comparisons, irrespective of whether or not and for how long they complied with their allocated regimen (intention-to-treat analysis)."
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	None

De Luis 2004

Methods	**Design:** blinded (information from author but not stated who was blinded), parallel-group randomised controlled trial with ≥ 10 days duration of treatment and 14 days duration of follow-up
Participants	**Setting:** author affiliations: Valladolid, Spain **Sample size:** • **Number randomised:** 90 • **Number completed:** 90 **Participant (baseline) characteristics:** • **Age:** mean age was 60.57 ± 12.3 years (60.2 ± 12.5 years in group 1 and 60.6 ± 11.5 years in group 2) • **Gender:** 6 females, 84 males • **Baseline differences/other characteristics:** Quote: "The characteristics of the patients on enrollment were similar for the two groups" **Inclusion criteria:** oral and laryngeal cancer **Exclusion criteria:** Quote: "Exclusion criteria included: severely impaired hepatic function (total bilirubin concentration > 3.5 mg/dl) and renal function (serum creatinine concentration > 2.5 mg/dl), ongoing infections, autoimmune disorders, steroids treatment, nutritional oral supplementation in previous 6 months, and severely malnourished (weight loss > 10% of body weight)."
Interventions	**Intervention group:** Enteral diet supplemented with arginine (n = 45) **Comparator group:** Isoenergetic, isonitrogenous enteral formula (n = 45) Enteral feeding was started within 12 hours of surgery

	Use of additional interventions: Quote: "In all patients, prophylactic antibiotic treatment was given for 7 days postoperatively (ceftazidime, 500 mg tid i.v. and clyndamicine 300 mg tid i.v.)"
Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "Perioperatively and on postoperative day 14 the following parameters were evaluated: serum values of prealbumin (mg/dl), transferrin (mg/dl), albumin (g/dl), and total number of lymphocytes (10^6 /ml). Postoperative complications were recorded as none, general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive unfiltration, temperature above 38.5°C and isolation of pathogens from the sputum or blood culture and/or urinary tract infection was diagnosed if the urine culture showed at least 10^5 colonies of a pathogen) , and wound complications such as fistula and/or wound infection. All complications were assessed with standard methods by the same investigator. Gastrointestinal problems related to enteral feeding were also recorded (diarrhoea, > 5 liquid stools in a 24-h period or an estimated volume > 2000 ml/day)."
Funding sources	None stated
Declarations of interest	None stated
Notes	**Participants lost to follow-up:** Quote: "No dropouts were present in the study" and an ITT analysis was conducted Quote: "The sample size was calculated to decrease 20% of fistula complication with 90% power and 5% significance."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author contacted: tables of random numbers used
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes used for allocation concealment (information from authors) but not known if envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States blinded (information from authors) but no indication as to who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States blinded (information from authors) but no indication as to who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data Quote: "all randomized patients were included in the comparisons, irrespective of

De Luis 2004 (*Continued*)

		whether or not and for how long they complied with their allocated regimen (intention-to-treat analysis)." Also stated "There were no dropouts due to intolerance"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Assessment of wound infection poorly described (Quote: "with standard methods by the same investigator") and no description of how length of stay was determined

De Luis 2005

Methods	**Design:** blinded (information from author but not stated who was blinded), parallel-group randomised controlled trial with an average duration of treatment of 20 days (in the supplemented group) and 6-day duration of follow-up
Participants	**Setting:** author affiliations: Valladolid, Spain **Sample size:** • **Number randomised:** 29 • **Number completed:** 29 **Participant (baseline) characteristics:** • **Age:** mean age was 61.1 ± 10.8 years (60.7 ± 11.6 years in group 1 and 62.96 ± 11.6 years in group 2) • **Gender:** 5 females, 24 males • **Baseline differences/other characteristics:** Quote: "Characteristics of the patients and tumour stage... on enrollment were similar for the two groups" **Inclusion criteria:** Quote: "patients with a previous weight loss of 5-10% (6 months), (IL-6 levels 45 pg/ml) and oral or laryngeal cancer were enrolled." **Exclusion criteria:** Quote: "Exclusion criteria included; severely impaired hepatic function (total bilirubin concentration > 3.5 mg/dl) and renal function (serum creatinine concentration > 2.5 mg/dl), ongoing infections, steroid treatment and well nourished (weight loss < 10% of body weight)."
Interventions	**Intervention group:** Enteral diet supplements with arginine (n = 14) **Comparator group:** Isocaloric, isonitrogenous enteral formula without arginine (n = 15) Quote: "Group I received a daily dose of arginine of 12.5 g during an average of 20 days" **Use of additional interventions:** none described
Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out Perioperatively and on postoperative day 6, the following blood parameters were evaluated: prealbumin (mg/dl), transferrin (mg/dl), albumin (g/dl), total number of lymphocytes (10^6 /ml), IL-6 (pg/ml), TNFa (pg/ml) and c-reactive protein (mg/dl)

De Luis 2005 (*Continued*)

Funding sources	None stated
Declarations of interest	None stated
Notes	**Participants lost to follow-up:** an ITT analysis was conducted. No postoperative deaths (information from authors)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author contacted: tables of random numbers used
Allocation concealment (selection bias)	Unclear risk	Quote: "At surgery, patients were randomly allocated (sealed envelops) to two groups" Also states that the study was a "prospective concealed randomized trial" but no statement on how concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Study was blinded" but no indication as to who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Study was blinded" but no indication as to who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data Quote: "all randomized patients were included in the comparisons, irrespective of whether or not and for how long they complied with their allocated regimen (intention-to-treat analysis)."
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	None

Felekis 2005

Methods	**Design:** parallel-group randomised controlled trial (no statement on blinding) with 6 days pre- and 8 days postoperative duration of treatment and unclear duration of follow-up
Participants	**Setting:** Greece **Sample size:** • **Number randomised:** 37

	• **Number completed:** 37 **Participant (baseline) characteristics:** • **Age:** not stated • **Gender:** not stated • **Baseline differences/other characteristics:** 35 were well nourished and 2 (1 in each group) were severely malnourished **Inclusion criteria:** patients undergoing major head and neck surgery (for cancer) **Exclusion criteria:** none stated
Interventions	**Intervention group:** Enteral immunonutrition for 6 days preoperatively and for 8 days postoperatively (n = 20) **Comparator group:** Regular oral diet and standard polymeric enteral feeding (n = 17) Quote: "Both groups received isocaloric and isonitrogenous regimens" **Use of additional interventions:** none stated
Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "The parameters analyzed were the incidence of postop. complications and mortality"
Funding sources	Not stated
Declarations of interest	Not stated
Notes	**Participants lost to follow-up:** not stated Note: abstract only. There is a linked reference: Felekis D, Eleftheriadou A, Papadakos G, Bosinakou I, Ferekidou E, Kandiloros D, et al. 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* 2010;62(8): 1105-12. We tried to contact the corresponding author by email and telephone but were unable to get a response using the information given in the above paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No statement on the generation of random sequence
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No statement on blinding

Felekis 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to judge from the published data (abstract only)
Selective reporting (reporting bias)	Unclear risk	Unable to judge from the published data (abstract only)
Other bias	Unclear risk	unable to judge from the published data (abstract only)

De Luis 2007

Methods	**Design:** blinded (information from author but not stated who was blinded), parallel-group randomised controlled trial with ≥ 10 days duration of treatment and 12 days duration of follow-up
Participants	**Setting:** author affiliations: Valladolid, Spain **Sample size:** • **Number randomised:** 72 • **Number completed:** 72 **Participant (baseline) characteristics:** • **Age:** mean age was 61.8 ± 13.3 years (62.1 ± 12 years in group 1 and 61.5 ± 11 years in group 2) • **Gender:** 7 females, 65 males • **Baseline differences/other characteristics:** epidemiological data for the patients on enrollment were similar for the 2 groups **Inclusion criteria:** patients with oral and laryngeal cancer **Exclusion criteria:** Quote: "Exclusion criteria included: severely impaired hepatic function (total bilirubin concentration > 3.5 mg/dl and serum glutamic pyruvate > 150 UI/l) and renal function (serum creatinine concentration > 2.5 mg/dl), ongoing infections, autoimmune disorders, steroids treatment, nutritional oral supplementation in previous 6 months and severely malnourished (weight loss > 10% of body weight)."
Interventions	**Intervention group:** Enteral diet supplements with arginine (n = 35) **Comparator group:** Isocaloric, isonitrogenous enteral formula (n = 37) Enteral feeding was started within 8 to 12 hours of surgery **Use of additional interventions:** Quote: "In all patients, prophylactic antibiotic treatment was given for 7 days postoperatively (ceftazidime, 500 mg t.i.d. intravenously (i.v.) and clyndamicine 300 mg t.i.d. i.v.)"
Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "Perioperatively and on postoperative day 12, the following parameters were

	evaluated: serum values of prealbumin (mg/ dl), transferrin (mg/dl), albumin (g/dl) and total number of lymphocytes (10^6 /ml). Postoperative complications were recorded as none; general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive unfiltration, temperature above 38.5°C and isolation of pathogens from the sputum or blood culture and/or urinary tract infection was diagnosed if the urine culture showed at least 10^5 colonies of a pathogen) and wound complications, such as fistula and/or wound infection, assessed all complications with standard methods by the same investigator surgeon. Gastrointestinal problems related to enteral feeding were also recorded (diarrhoea, > 5 liquid stools in a 24-h period or an estimated volume > 2000 ml/day)."
Funding sources	Not stated
Declarations of interest	Not stated
Notes	**Participants lost to follow-up:** stated that an ITT analysis was conducted and "No drop-outs were present in the study" Quote: "Sample size was calculated to decrease 25% of wound complication with 90% power and 5% significance."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Author contacted: tables of random numbers used
Allocation concealment (selection bias)	Unclear risk	Envelopes (information from authors) but not known if these were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding stated (information from authors) but no indication as to who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding stated (information from authors) but no indication as to who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data: Quote: "all randomized patients were included in the comparisons, irrespective of whether or not and for how long they complied with their allocated regimen (intention-to-treat analysis)." Also stated "There were no dropouts due to intolerance"
Selective reporting (reporting bias)	Unclear risk	Protocol not available

De Luis 2007 (*Continued*)

Other bias	High risk	Assessment of wound infection poorly described (Quote: "with standard methods by the same investigator surgeon") and no description of how length of stay was determined

Casas-Rodera 2008

Methods	**Design:** parallel-group randomised controlled trial (no statement on blinding) with average duration of treatment of 14.5 ± 8 days and 14 days duration of follow-up
Participants	**Setting:** La Paz University Hospital, Spain. Trial carried out for 12 months **Sample size:** • **Number randomised:** 44 • **Number completed:** 44 **Participant (baseline) characteristics:** • **Age:** group 1: 59.67 ± 9.07, group 2: 54.27 ± 13.04, group 3: 50.07 ± 13.79 • **Gender:** group 1: 13 men, 2 women, group 2: 15 men, 0 women, group 3: 14 men, 0 women • **Baseline differences/other characteristics:** Quote: "The characteristics of the patients on enrolment were similar for the three groups, reflecting the homogeneity of patients. There were no significant differences with respect to gender, mean age, body weight, location, and stage of tumor" **Inclusion criteria:** oral and laryngeal cancer **Exclusion criteria:** Quote: "Severely impaired hepatic function (total bilirubin concentration over 43.5 mg/dl) and renal function (serum creatinine concentration over 42.5 mg/dl), ongoing infections, autoimmune disorders, steroids treatment, nutritional oral supplementation in previous 6 months."
Interventions	**Intervention group:** Group 1 (enteral diet supplemented with arginine) (n = 15) Group 3 (enteral diet supplemented with arginine, RNA and omega-3 fatty acids) (n = 14) **Comparator group:** Group 2 (standard polymeric enteral formula) (n = 15) Quote: "Enteral feeding was started within 12 h of surgery, via an intraoperatively placed nasogastric tube." **Use of additional interventions:** none stated
Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "Perioperatively and on postoperative day 7 and day 14 the following parameters were evaluated: serum values of transferrin (mg/dl), albumin (g/dl), and total number of lymphocytes (10^6/ml), IL-6 (mg/dl), TNFa (pg/dl) and CPR (mg/dl). Postoperative complications were recorded as none, general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive infiltration, temperature above 38.5 ºC and isolation of pathogens from the sputum or blood culture and/or urinary tract infection was diagnosed if the urine culture showed at least

	10^6 colonies of a pathogen), and wound complications such as fistula and/or wound infection. All complications were assessed with standard methods by the same investigator. Gastrointestinal problems related to enteral feeding were also recorded (diarrhoea, > 5 liquid stools in a 24-h period or an estimated volume > 2,000 ml/day). The duration of hospitalisation was based on the date that the patient was medically eligible for discharge. "
Funding sources	None stated
Declarations of interest	None stated
Notes	**Participants lost to follow-up:** Quote: "No dropouts were present in the study" The comparison used is group 2 (standard polymeric feed) and group 3 (arginine, RNA and omega-3 fatty acids). Data from group 1 (arginine only) were not used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "At surgery, patients were randomly allocated to three groups" but does not say how sequence was generated
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No statement on blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data Quote: "No dropouts were present in the study"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Assessment of wound infection poorly described (Quote: "with standard methods by the same investigator")

Sorensen 2009

Methods	**Design:** double-blind (NB: some outcome assessors not blinded - see Table 3 for more information), parallel-group randomised controlled trial with 7 days pre- and 7 days postoperative duration of treatment and 29 days duration of follow-up
Participants	**Setting:** Department of Surgery, Otolaryngology - Head and Neck Surgery Service, Madigan Army Medical Center, Tacoma, Washington, USA **Sample size:** • **Number randomised:** 15 • **Number completed:** 15 **Participant (baseline) characteristics:** • **Age:** mean age 60.6 years (SD 8.2, range 46 to 73 years), group 1 mean age 61.9 years (SD 8.5, range 46 to 73 years), group 2 mean age 58.9 years (SD 7.4, range 48 to 67 years) • **Gender:** all male • **Baseline differences/other characteristics:** Quote: "Nutritional status was similar for patients in both groups upon enrollment. Baseline values of height, weight, body mass index, weight loss in previous 6 months, subjective global assessment, nutritional risk, albumin, and prealbumin showed no statistically significant differences." and "Immunologic measures...of white blood cell, TLC, and lymphocyte subsets were not different between groups at baseline. CRP did not pass Levene's test for equality of variances at baseline (P = .023), but was not statistically significantly different between groups" **Inclusion criteria:** age > 18 years, histologically documented squamous cell carcinoma of the head and neck, candidates for curative surgery **Exclusion criteria:** history of renal, hepatic or cardiopulmonary dysfunction, ongoing infection and immune deficiency
Interventions	**Intervention group:** Impact Recover oral drink or Impact Glutamine tube feeding (Novartis Nutrition) (n = 8) **Comparator group:** Standard supplement (Isosource 1.5 from Novartis Nutrition) (n = 7) Participants received/were asked to drink about 1 L per day for 7 days preoperatively and 7 days postoperatively. Postoperative feeding began within 24 hours post surgery **Use of additional interventions:** none stated
Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out The following were measured at baseline, day of surgery and postoperative days 1, 4 and 8: complete blood count, total lymphocyte count, T-lymphocyte subsets (CD3, CD4, CD8, CD4:8 ratio, CD19, CD56), albumin, prealbumin and CRP. Cell mediated immunity was evaluated by delayed-type hypersensitivity. Serious wound complications included wound infection, wound dehiscence and wound fistula. Wound assessments used the ASEPSIS scoring method
Funding sources	Quote: "Sponsored by the TriService Nursing Research Program and supported by a grant of $35,884."
Declarations of interest	None stated

Sorensen 2009 (*Continued*)

Notes	**Participants lost to follow-up:** no statement about dropouts. Few participants completed the delayed-type hypersensitivity (DTH) skin test Power/sample size calculation not done as it was a feasibility study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to have a "Randomized design" but no statement on the generation of the random sequence
Allocation concealment (selection bias)	Unclear risk	Envelopes used but not known if these were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The principal investigator and otolaryngology head and neck service residents were blinded to study group, an associate investigators (AI) and research assistant (RA) were not."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The principal investigator and otolaryngology head and neck service residents were blinded to study group, an associate investigators (AI) and research assistant (RA) were not."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement on dropouts
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	None

De Luis 2009

Methods	**Design:** double-blind, parallel-group randomised controlled trial with ≥ 10 days duration of treatment and 10 days duration of follow-up
Participants	**Setting:** author affiliations: Valladolid, Spain **Sample size:** • **Number randomised:** 72 • **Number completed:** 72 **Participant (baseline) characteristics:** • **Age:** mean age was 62.3 ± 11.3 years (63.1 ± 13 years in group 1 and 61.2 ± 9.9 years in group 2) • **Gender:** 15 females, 57 males (8 females, 30 males in group 1 and 7 females, 27 males in group 2)

	• **Baseline differences/other characteristics:** "Epidemiological data of the patients on enrollment were similar for the two groups, reflecting the homogeneity of patients. There were no significant differences with regard to gender, mean age, body weight, location, and stage of tumor" **Inclusion criteria:** oral and laryngeal cancer **Exclusion criteria:** Quote: "Exclusion criteria included: severely impaired renal function (serum creatinine concentration > 2.5 mg/dl) and hepatic function (total bilirubin concentration > 3.5 mg/dl and serum glutamic pyruvate > 150 UI/l), ongoing infections, autoimmune disorders, steroids treatment, nutritional oral supplementation in previous 6 months and severely malnourished (weight loss > 10% of body weight)"
Interventions	**Intervention group:** Enteral diet supplements with arginine and fibre (n = 38) **Comparator group:** Isocaloric, isonitrogenous enteral formula (n = 34) Quote: "Enteral feeding was started within 24 hours of surgery" **Use of additional interventions:** Quote: "In all patients, prophylactic antibiotic treatment was given for 7 days postoperatively (ceftazidime, 500 mg t.i.d. intravenously (i.v.) and clyndamicine 300 mg t.i.d. i.v.)."
Outcomes	**Primary outcome and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "Perioperatively and on postoperative day 10, the following parameters were recorded: serum values of prealbumin (mg/dl), transferrin (mg/dl), albumin (g/dl), total number of lymphocytes (10^6 /ml). Postoperative complications were registered as none; general infections (urinary tract infection was diagnosed if the urine culture showed at least 10^5 colonies of a pathogen and/or respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive unfiltration, temperature above 38,5°C and isolation of pathogens from the sputum or blood culture) and local complications such as fistula and/or wound infection, assessed all complications with standard methods by the same investigator. Gastrointestinal problems related to enteral feeding were also recorded (diarrhoea, > 5 liquid tools in a 24-hour period or an estimated volume > 2000 mL/d)." Data on length of stay were also presented
Funding sources	None stated
Declarations of interest	None stated
Notes	**Participants lost to follow-up:** stated that an ITT analysis was conducted Quote: "Sample size was calculated to decrease 20% of wound complication with 80% power and 5% significance."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

De Luis 2009 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "At surgery, patients were randomly allocated to two groups", but no statement on the generation of random sequence
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Main investigator and patients remained blind to the treatment group."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Main investigator and patients remained blind to the treatment group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data Quote: "all randomized patients were included in the comparisons, irrespective of whether or not and for how long they complied with their allocated regimen (intention-to-treat analysis)." Also stated "There were no drop outs due to intolerance"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Assessment of wound infection poorly described (Quote: "with standard methods by the same investigator") and no description of how length of stay was determined

Felekis 2010

Methods	**Design:** double-blind, parallel-group randomised controlled trial with 5 days pre- and 8 days postoperative duration of treatment and 8 days duration of follow-up
Participants	**Setting:** First Department of Otolaryngology, University of Athens, Greece **Sample size:** • **Number randomised:** 40 • **Number completed:** 40 **Participant (baseline) characteristics:** • **Age:** mean age 62.1 ± 2.6 years, group 1 mean age 63.2 ± 3.9 years, group 2 mean age 61.0 ± 3.8 years • **Gender:** 4 females, 36 males (2 females and 18 males in each of the 2 treatment groups) • **Baseline differences/other characteristics:** Quote: "Characteristics of the patients on enrollment were similar for the two groups" and "There were no significant differences with regard to gender, mean age, nutritional status, location, and stage of the disease." Also stated that there were no baseline differences in the outcome variables. **Inclusion criteria:** Quote: "In all cases, there was a histologically proven diagnosis of

	squamous cell carcinoma of head and neck eligible for surgical treatment. No previous radiotherapy or chemotherapy was applied. Patients did not receive immunoglobulin before the study." **Exclusion criteria:** Quote: "Exclusion criteria included severely impaired renal and hepatic function and autoimmune disorders."
Interventions	**Intervention group:** Oral Impact (Novartis) for 5 days pre-operatively and enteral Impact for 8 days postoperatively (n = 20) **Comparator group:** No pre-operative nutritional support and enteral Nutrison (Nutricia) for 8 days postoperatively (n = 20) Quote: "The immuno-enhanced formula was incorporated in a way that caloric equivalence between Groups 1 and 2 was preserved." Enteral feeding was started within 24 hours of surgery **Use of additional interventions:** none stated
Outcomes	**Primary and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "Five days before and 8 days after surgery the following parameters were evaluated: Albumin (g/dl), prealbumin (mg/dl), fibrinogen (mg/dl), and C-reactive protein (CRP; mg/dl), Il-6 (pg/ml), and TNF-α (pg/ml) by ELISA." Postoperative complications were also assessed but not mentioned in the methods. Results that were presented suggest that the following were assessed: minor complications (increase of temperature), major complications (pneumonia, urinary tract infection, fistula, wound infection)
Funding sources	Quote: "The authors declare that there is no conflict of interest and no funding also."
Declarations of interest	Quote: "The authors declare that there is no conflict of interest and no funding also."
Notes	**Participants lost to follow-up:** Quote: "No dropouts occurred because of intolerance" Of the 40 participants, 30 were considered well nourished (< 10% weight loss in last 6 months) and 10 malnourished (> 10% weight loss in last 6 months). Subgroup analyses conducted with the 30 well nourished participants and the 10 malnourished participants No description of how the postoperative complications were assessed. We tried to contact the corresponding author by email and telephone but were unable to get a response using the information given in the paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was based on known techniques (using a randomization generator)."

Allocation concealment (selection bias)	Unclear risk	Quote: "We generated a series of random numbers that ranged from 1 to 32 for operated patients for the larynx- or hypopharynx-sited tumours and 1 to 8 for operated patients for the oral cavity or tongue-sited tumours. We then tabulated the two series according to their randomization rating. We assigned the solution for each number, following the randomized sequence, using an alternating mode. Patients were numbered from 1 to 32 if they were in the first category according to the site of the tumour, and from 1 to 8 for the second category, following the sequence of their arrival, and they were introduced to the solution according to the randomization table. " The authors also stated that they monitored the distribution of gender and age within groups, but observed no difference (and did not need to interrupt the randomisation procedure to balance the groups with respect to these 2 parameters)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated "double-blinded" in the methods section but no indication as to who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated "double-blinded" in the methods section but no indication as to who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data: no loss to follow-up described Quote: "No dropouts occurred because of intolerance"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Assessment of complications (wound infection) poorly described

Ghosh 2012

Methods	**Design:** double-blind, parallel-group randomised controlled trial with 5 days pre- and 7 days postoperative duration of treatment and 30 days duration of follow-up
Participants	**Setting:** Aintree University Hospitals NHS Foundation Trust, Liverpool, UK. Patients randomised between November 2005 and July 2008 **Sample size:** • **Number randomised:** 60 • **Number completed:** 57 **Participant (baseline) characteristics:** • **Age:** median age was 62 (IQR 57 to 65) in the Impact group and 60 (IQR 53 to 66) in the control group • **Gender:** 50 males (24 in Impact group, 26 in control group), 7 females (4 in Impact group, 3 in control group) • **Baseline differences/other characteristics:** some imbalances were anticipated and confirmed: the Impact group had more patients with oral cavity tumours, more with later stage tumours and less co-morbidity **Inclusion criteria:** Quote: "Eligible patients were those with advanced squamous cell carcinoma of the oral cavity, oropharynx, larynx or hypopharynx, for whom surgery +/- adjuvant radiotherapy or chemoradiotherapy had been decided upon as the treatment of choice and for whom enteral feeding was considered appropriate. Previous radiotherapy was not an exclusion criterion." **Exclusion criteria:** Quote: "Specific exclusion criteria included patients with malabsorption syndromes; primary immune disorders; active infection on presentation; patients undergoing secondary surgical reconstruction; patients aged under 18 years, and patients who were pregnant or breast feeding."
Interventions	**Intervention group:** Impact (Nestlé Healthcare Nutrition, Minnetonka, MN, USA) - contains supplemental L-arginine (1.25 g/L), dietary nucleotides (1.2 g/L) and omega-3 fatty acids in the form of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (EPA/DHA 1.7 g/L) (n = 28) **Comparator group:** Isocaloric isonitrogenous control feed manufactured for the trial (n = 29) The feed was given enterally by NG or PEG tube (to enhance blinding) for 5 days pre- and 7 days post-surgery Quote: "The target duration and rate of feeding was 500 ml/day for 5 days pre-surgery and 1 L/day for 7 days post-surgery. Patients, who were able, were allowed to eat or drink in addition to their supplemental enteral feeds." **Use of additional interventions:** none stated
Outcomes	**Primary outcome:** Quote: "The primary outcome event was defined as any patient with an infection of the lower respiratory tract, gastro-intestinal tract, urinary tract or blood which required antibiotic treatment and occurred at any time, up to the 30th post-operative day." Quote: "surgical site/wound infections were defined according to CDC Definitions of Nosocomial Surgical Site infections, 1992, and the ASEPSIS wound score. The diagnosis of the non-wound infection was as stipulated in the Trial Antibiotic Policy" **Secondary outcomes:** Quote: "Secondary outcome measures included infections of primary surgical site, neck wound, PEG site, tracheostomy, free-flap or split skin graft donor site and the length of hospital stay e defined as the time from surgery to the date

Ghosh 2012 (*Continued*)

	when the patient was deemed medically fit for discharge."
Funding sources	Quote: "Nestlé Healthcare Nutrition provided the control and experimental feeds, together with the giving sets free of charge. Novartis UK granted £4000 towards the running costs of the trial."
Declarations of interest	Quote: "Neither do any of the authors have any other potential conflict of interest to declare."
Notes	**Participants lost to follow-up:** 3 early withdrawals (post-randomisation). Quote: "One who stopped feeding following the decision to proceed with radical radiotherapy rather than surgery; one was deemed inoperable following clinical review after randomisation, and one patient opted to withdraw."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The Trust Pharmacy Clinical Trials Unit generated randomisation lists
Allocation concealment (selection bias)	Low risk	Quote: "The allocation of patients to trial groups was administered independently by the Trust Pharmacy Clinical Trials Unit using randomisation lists which were stratified on the basis of clinical specialty to whom the patient presented (Otorhinolaryngology/Head and Neck Surgery or Maxillofacial Surgery) and whether patients had previously received radiotherapy or not."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To enhance blinding, and allow a more accurate assessment of compliance, both groups were fed enterally, either by nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) feeding tube depending on clinical appropriateness. Feed bottles containing either Impact or control feed were packaged identically."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated that study personnel were blinded (feed bottles were packaged identically and both groups fed enterally)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Stated that an ITT analysis was conducted. Also states that "Of the 60 patients randomised there were three early withdrawals: One who stopped feeding following the de-

Ghosh 2012 (*Continued*)

		cision to proceed with radical radiotherapy rather than surgery; one was deemed inoperable following clinical review after randomisation, and one patient opted to withdraw". NB: length of stay analysis "excludes 4 patients who died as inpatients, 3 from the Impact group (LOS 18, 22 & 32 days) and 1 from the control group (LOS 30 days)"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Sample size calculation done, but "The trial was discontinued before achieving the calculated sample size as our rate of recruitment was insufficient to enable study completion in a practical time-frame and in the absence of funding to allow the inclusion of additional centres." Also quoted that "some imbalances were anticipated and confirmed: the Impact group had more patients with oral cavity tumours, more with later stage tumours, and less co-morbidity."

Turnock 2013

Methods	**Design:** non-blinded, parallel-group randomised controlled trial with 5 days pre- and ≥ 5 days postoperative duration of treatment and duration of follow-up to hospital discharge
Participants	**Setting:** head and neck outpatient clinics at Auckland City Hospital, New Zealand. Carried out between May 2007 and January 2008 **Sample size:** • **Number randomised:** 8 • **Number completed:** 8 **Participant (baseline) characteristics:** • **Age:** ranged from 28 to 68 years in the immunonutrition group and from 17 to 79 years in the control group • **Gender:** 6 males (3 per treatment group) and 2 females (1 per treatment group) • **Baseline differences/other characteristics:** not specifically reported, but no major differences reported/presented in the paper **Inclusion criteria:** Quote: "patients who were scheduled for radical resection of the oral cavity, pharynx or larynx and who were expected to require artificial feeding by the enteral route postoperatively." **Exclusion criteria:** Quote: "Patients were excluded if they were: aged < 16 year, malnourished (weight loss ≥ 10% of body weight within the last 6 months), had undergone previous wide-field radical radiotherapy, or were pregnant, diabetic or immuno-

	suppressed.“
Interventions	**Intervention group:** Preoperative oral Impact and postoperative enteral Impact (n = 4) Quote: ”IMN patients were provided with three 74 g sachets per day of powdered Oral Impact® (Novartis Consumer Health, Nyon, Switzerland) to be taken for 5 days immediately preceding day of surgery“ and IMN patients received enteral Impact® (Novartis) post-operatively. If tube feeding was discontinued, nutritional support was continued with Oral Impact until at least POD5.” **Comparator group:** Patients did not receive preoperative nutritional supplement and received standard hospital enteral nutrition (Isosource Standard®, Novartis) postoperatively (n = 4) Postoperative feeding began as soon as tolerated via an intraoperatively placed nasogastric tube **Use of additional interventions:** Quote: “Prophylactic antibiotic treatment was given to all patients for 7 days postoperatively.”
Outcomes	**Primary and secondary outcomes:** Primary and secondary outcomes not separated out Blood samples taken at baseline, day of surgery, immediately preceding induction of anaesthesia and on postoperative days (POD) 2, 4 and 10: measured for plasma fatty acids, immunoglobulins (A, G and M), inflammatory markers (tumour necrosis factor (TNF)-α, interleukin (IL)-6 and IL-10, and C-reactive protein) and full blood count determinations Quote: “Assessment of clinical outcome was undertaken until discharge and included postoperative complications and length of hospital stay. General infections (urinary tract infection, respiratory tract infection), flap anastomosis complications (venous or arterial) , and wound complications (dehiscence, tissue necrosis, haematoma, chyle leak, salivary fistula or wound infection) were recorded. Infectious complications were judged using CDC criteria and were considered significant if antibiotic therapy was instituted.”
Funding sources	Quote: “This study was supported by a grant from the Greenlane Research and Educational Fund”
Declarations of interest	Quote: “LDP has received funding support from Novartis/Nestle, Nutricia and Abbott Laboratories, and honoraria from Baxter Healthcare. PCC is a consultant to Danone Research Center for Specialised Nutrition and Pronova Biopharma; has received speaking honoraria from Fresenius Kabi, B. Braun, Baxter Healthcare, Abbott Nutrition, and Nestle; and has research funding from Abbott Nutrition. The authors report no other conflicts of interest.”
Notes	**Participants lost to follow-up:** none stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Turnock 2013 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "The allocation sequence was derived from a computer-generated random enumeration."
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was non-blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was non-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition according to number of participants included in results
Selective reporting (reporting bias)	High risk	Not all primary outcomes stated in the protocol were presented (data for CD3, CD4 and CD8 were not included in the manuscript). Additional outcomes to those stated in the protocol were presented in the manuscript (IL-10, length of stay, EPA, DHA, AA)
Other bias	High risk	Target sample size was 30 (15 per treatment group); only recruited 8

De Luis 2014

Methods	**Design:** double-blind, parallel-group randomised controlled trial with minimum of 15 days duration of treatment and 10 days duration of follow-up
Participants	**Setting:** author affiliations: Valladolid, Spain **Sample size:** • **Number randomised:** 82 • **Number completed:** 82 **Participant (baseline) characteristics:** • **Age:** mean age 64.6 years (SD 11.4) • **Gender:** male n = 72, female n = 10 • **Baseline differences/other characteristics:** no differences at baseline in age, gender, weight, tumour location or stage **Inclusion criteria:** Quote: "The study protocol was designed to study patients with head and neck cancer after a surgery in abcense of type 2 diabetes mellitus or alteration of fasting glucose, diagnosed by fasting plasma glucose less than 110 mg/ dl." and "All patients have a histologically proven squamous cell carcinoma of the oral cavity, larynx, oropharyns or hypopharynx and required major ablative surgery." **Exclusion criteria:** Quote: "Patients were excluded from the study if they were impaired

	renal function (serum creatinine concentration > 2.5 mg/ dl), ongoing infections, autoimmune disorders, steroids treatment, nutritional oral supplementation in previous 6 months and severely malnourished (weight loss > 10% of body weight)."
Interventions	**Intervention group:** Group 1 received an enteral diet supplements with a high dose of L-arginine (20 g per day) (n = 42) **Comparator group:** Group 2 received an isocaloric, isonitrogenous enteral formula without L-arginine (n = 40) Both groups were tube fed for 15 days post surgery. The rate of feed was increased so the target rate of 35 kcal/kg (1.7 g protein/kg) was reached within 4 days **Use of additional interventions:** none stated
Outcomes	**Primary and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "At basal time and on postoperative day 10, the following parameters were recorded: glucose, c-reactive protein (CRP), insulin, HOMA (homeostasis model assessment), leptin and adiponectin." Also measured weight, waist and hip circumferences, and body composition via bioelectrical impedance, and reported on BMI
Funding sources	None declared
Declarations of interest	None declared
Notes	**Participants lost to follow-up:** Quote: "No drop-outs were present in the study" **Outcomes:** no relevant outcomes for this review **Other:** stated that an ITT analysis was conducted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned" but no other information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding of patients and dietitians involved in patient treatment was maintained"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Blinding of patients and dietitians involved in patient treatment was maintained", but no indication of who outcome assessor was

De Luis 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data Quote: "No drop-outs were present in the study"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	None

Falewee 2014

Methods	**Design:** double-blind, parallel-group randomised controlled trial with 7 days pre- and 7 to 15 days postoperative duration of treatment and 90 days duration of follow-up
Participants	**Setting:** 8 centres in France; conducted between July 2007 and April 2011 **Sample size:** • **Number randomised:** 298 • **Number completed:** 205 **Participant (baseline) characteristics:** • **Age:** Group A: 59.5 (SD 9.6) years, group B: 59 (SD 9.7) years, group C: 58.2 (SD 8.7) years • **Gender:** Group A: 12 female, 52 male, group B: 11 female, 57 male, group C: 10 female, 63 male • **Baseline differences/other characteristics:** no evidence of baseline differences between groups **Inclusion criteria:** Quote: "To enter the study, patients must have confirmed squamous cell carcinoma of the oral cavity, oropharynx, larynx or hypopharynx, with anticipated surgery and postoperative enteral feeding for a minimum of seven days. They had to be aged ≥ 18 and ≤ 75, with adequate hematopoietic function [absolute neutrophil count > 1.8 10^9 /l, haemoglobin level ≥ 9 g/dl], adequate hepatic function [total serum bilirubin, serum aminotransferases ≤ 3 x institutional upper limit of normal (ULN)], and adequate renal function [serum creatinine ≤ 2 ULN], urea ≤ 1.5 ULN], glucose < 1.5 g/L, sodium < 145 mmol/L." **Exclusion criteria:** Quote: "Ineligible patients included: patients treated with neo-adjuvant chemotherapy, radiation therapy delivered on head and neck area during the previous year, patients having received oral supplements containing immune nutrients before study entry, patients testing positive for HIV, pregnant or breast-feeding women."
Interventions	**Intervention group:** Group B: pre-operative Impact and postoperative standard diet (n = 68) Group C: pre- and postoperative Impact (n = 73) **Comparator group:** Group A: control, i.e. 'standard diet' - Impact without immune nutrients that had been manufactured for the study (n = 64) Pre-operatively: Quote: "For seven days before surgery, well-nourished patients with no dysphagia received three sachets per day of nutrition according to the randomization (Oral Impact or standard diet). Each sachet dissolves in 250 ml of water and represents 303 kcal and 2.88 g of nitrogen. Patients with severe malnutrition or presenting a significant dysphagia received standard enteral nutrition according to their needs (French

	recommendations). Seven days before surgery, they switched 1000 kcal from their intake to the investigational nutrition according to the randomization." Postoperatively: Quote: "For a minimum of 7 days and a maximum of 15 days after surgery, all patients received enteral nutrition according to randomization" **Use of additional interventions:** "Antibiotic prophylaxis was allowed for 24 h following the surgery, according to the guidelines published in 1998." Randomly allocated to 3 groups: a) perioperative formula of Impact without immune nutrients, named "reference diet" (group A, control); b) preoperative Impact and "reference diet" postoperatively (group B); c) Impact perioperatively (group C)
Outcomes	**Primary outcome:** Infectious complications Quote: "The primary outcome event was defined as any patient with a systemic infection requiring antibiotic treatment (septicaemia, bacteraemia), surgical site infection (according to CDC Definitions of Nosocomial Surgical Site infections), documented nosocomial pneumopathy, up to the 30th post-operative day. It was named 'infectious complications' (IC)." **Secondary outcomes:** Surgical site infections and length of hospital stay Quote: "Secondary outcome measures included: surgical site infections (SSI) (primary surgical site, neck wound, free-flap or split skin graft donor site, and tracheotomy) and length of hospital stay (LOS) defined as the time from surgery to the date when the patient was deemed medically fit for discharge."
Funding sources	Quote: "Nestlé Health Science, Switzerland kindly supplied Impact and the formula of Impact without immune nutrients. The study was supported by grants from the French National Cancer Institute (Hospital Clinical Research Program 2006)."
Declarations of interest	Quote: "PB has perceived honoraria from Nestlé as member of the scientific board of the journal Nutrizoom until December 2012."
Notes	**Participants lost to follow-up:** extra data obtained to enable intention-to-treat analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was centralized and carried out by the CS RANDOMIZATION module from Clinsight software. The stratification consisted of searching with an algorithm, for the less-often allocated treatment code among patients whose randomisation criteria matched the ongoing patient."
Allocation concealment (selection bias)	Low risk	Quote: "To ensure the blinding of study personnel, the allocation of patients to trial groups was carried out independently by

Falewee 2014 (*Continued*)

		the Pharmacy Clinical trials Units using randomisation lists."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blinding with adequate labels was used to minimize bias with bedside physicians and nurses."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blinding with adequate labels was used to minimize bias with bedside physicians and nurses."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Manuscript did not present an ITT analysis, but additional data obtained from authors to enable ITT analysis to be conducted
Selective reporting (reporting bias)	Low risk	Rate of infectious complications stated as a primary outcome in the protocol (see: https://clinicaltrials.gov/show/NCT00765440) and presented in the manuscript. No secondary outcomes specified in protocol
Other bias	High risk	Quote: "The recruitment was discontinued in April 2011 before reaching the calculated sample size. The rate was too low to enable study completion in the scheduled time frame and with the funding received. "

Azman 2015

Methods	**Design:** non-blinded, parallel-group randomised controlled trial with 4 weeks duration of treatment and 4 weeks duration of follow-up
Participants	**Setting:** Department of Otorhinolaryngology and Oral and Maxillofacial Surgery, Universiti Kebangsaan Malaysia Medical Centre, between January 2011 and June 2012 **Sample size:** • **Number randomised:** 46 • **Number completed:** 44 Quote: "One patient (control group) had to be excluded from the study as the patient died during the study period, and the other requested to be withdrawn from the study." Additional information was provided on the latter patient within the discussion section of the manuscript. Quote: "Only 1 patient had persistent diarrhea and abdominal discomfort after supplementation, hence, requested to be discontinued from supplements. The abdominal side effects resolved completely after a day of discontinuation from treatment and this patient was excluded from the study." **Participant (baseline) characteristics:** • **Age:** median age 49 years (range 22 to 74)

	• **Gender:** 24 male, 20 female • **Race:** 26 were Malays (59.1%), 14 were Chinese (31.8%) and 4 were Indians (9.1%) • **Baseline differences/other characteristics:** no differences in baseline demographics **Inclusion criteria:** Quote: "Patients diagnosed as having any head and neck malignancy being scheduled for surgery to address primary tumor site or nodal disease (clinical staging of tumor based on American Joint Committee on Cancer staging T1-4, N0-3, and M0). Patients age 20 to 75 years old." **Exclusion criteria:** Quote: "Those contraindicated to enteral nutrition (maldigestion or malabsorption, such as in gut, atonia, ileus). Severe liver (serum bilirubin > 30 mmol/L or serum alanine transaminase > 100 IU/L or serum alkaline phosphatase > 200 IU/L) or renal insufficiency (serum urea > 20 mmol/L, serum creatinine > 300 mmol/L, or urine output < 500 mL/day). Severe malnutrition not amendable to enteral nutritional optimization (patients who cannot swallow at all and refuse any form of enteral feeding via Ryle's tube, gastrostomy, and jejunostomy tubes with fat-free mass < 14.6 kg/m² in men or < 11.4 kg/m² in women or serum albumin of < 15 g/dL). Severe cancer cachexia or sarcopenia (fat-free mass < 14.6 kg/m² in men or < 11.4 kg/m² in women or serum albumin of < 15 g/ dL). Patients with inborn errors of metabolism of nutrients contained in Glutamine Plus. Patients with head and neck malignancy going for chemoradiotherapy, including patients who are irradiated while on glutamine supplementation. Patients with head and neck malignancy who had any form of concurrent treatment protocols (hormonal, alternative, antiviral, or photodynamic therapy) during the study duration."
Interventions	**Intervention group:** Glutamine Plus (Fresenius Kabi, Bad Homburg, Germany), 10 g 3 times a day for 4 weeks post surgery (n = 22) **Comparator group:** No supplement (n = 22) Patients in both groups received protein/calorie optimisation from dietary modifications as well as nutritional supplements
Outcomes	**Primary and secondary outcomes:** Primary and secondary outcomes not separated out Quote: "At the first visit, which was before surgery, demographic data, fat-free mass measurement using body impedance analysis, quality of life score, serum albumin measurement, and daily caloric intake (via 24-hour dietary recall) were assessed. At the end of 4-week duration, which corresponded to 4 weeks postsurgery, the investigator assessed the patients recruited to both groups with regard to 24-hour dietary recall, quality of life scores, serum albumin, and body composition analysis." NB: data included: age, sex, race, cancer type, staging, surgical procedures performed, height, weight and liver function (assessed at baseline and 4 weeks)
Funding sources	Quote: "Contract grant sponsor: Universiti Kebangsaan Malaysia Fundamental Grant"
Declarations of interest	None declared

Notes	**Participants lost to follow-up:** Quote: "One patient (control group) had to be excluded from the study as the patient died during the study period, and the other requested to be withdrawn from the study." (The latter patient was from the intervention group and was due to diarrhoea) **Other:** • Overall compliance was 94.4% • Quote: "The sample size calculation for this interventional study was performed using Power and Sample Size (PS3) software (2009) by Dupont and Plummer from Vanderbilt University. The method used was the formula for prospective studies with dichotomous outcome and analyzed by t tests. Forty-four patients with 22 patients from the interventional population were needed to make the study statistically significant with 95% confidence intervals to detect significant differences between the control and interventional groups." • Quote: "Patients in both groups received protein calorie optimization from dietary modifications as well as nutritional supplements, such as Nutren Optimum (Nestle, South Africa), Glucerna (Abbott Laboratories, United States), and Myotein (Pharm-D, Malaysia), where applicable."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The method of randomization was random ballot picking of sealed envelopes that were assigned numbers from 1 to 44. Odd numbers meant recruitment into the control group and even numbers meant recruitment into the interventional group."
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes used (but not known if these were opaque)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No blinding was used"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "No blinding was used"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated whether any dropouts occurred and unclear how many data points are included in each figure
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	None

Hanai 2018

Methods	**Design:** parallel-group randomised controlled trial (not stated if blinded) with 14 days pre- and 14 days postoperative duration of treatment and 14 days duration of follow-up
Participants	**Setting:** author affiliations: Department of Head and Neck Surgery, Aichi Cancer Center Hospital, Nagoya, Aichi, and Department of Otorhinolaryngology, Head and Neck Surgery, Graduate School of Medicine, University of the Ryukyus, Nishihara, Okinawa, Japan **Sample size:** • **Number randomised:** 28 • **Number completed:** 27 **Participant (baseline) characteristics:** • **Age:** average age was 61.5 (range 45 to 77) years in the intervention group and 66.1 (range 47 to 76) years in the comparator group • **Gender:** 16 male (8 per treatment group), 11 female (5 in the intervention group and 6 in the comparator group) • **Baseline differences/other characteristics:** Quote: "There were no significant differences in the background factors of the patients in the two arms". Authors also quoted "Seven of the 13 patients in the experimental arm and 8 of the 14 patients in the control arm received preoperative chemotherapy." **Inclusion criteria:** Quote: "patients undergoing head and neck cancer surgery who required resection and free flap reconstruction and who exhibited ≥ 5% weight loss". Quote: "Eligibility criteria: (1) histopathologically diagnosed head and neck squamous cell carcinoma, (2) indication for free flap reconstruction, (3) the subject intended to participate in this test and provided their written consent, (4) the age at the time of registration was 20-80 years, (5) an ECOG performance status of 0-2, (6) ≥ 5% weight loss within the past 6 months, (7) life expectancy ≥6 months and (8) the patient's major organ function was maintained." **Exclusion criteria:** Quote: "Patients who met any of the following exclusion criteria were excluded from the study: (1) intestinal occlusion and serious enterostenosis (enteral feeding intolerance), (2) combined resection of other organs, (3) obvious focal infection before surgery, (4) serious heart, liver or kidney disease, (5) uncontrolled diabetes, (6) refractory hyperlipemia, (7) a past history of chronic inflammatory disease, (8) continuous or general administration (oral or intravenous) of steroids, (9) subjects taking EPA, (10) a past history of anaphylaxis against components of Prosure® (e.g. milk and soybean) , (11) patients who are pregnant, lactating or possibly pregnant and (12) patients who were deemed ineligible for other reasons by the principal investigator of the test."
Interventions	**Intervention group:** Prosure® (an eicosapentaenoic acid (EPA)-enriched oral nutritional supplement) was administered at a dose of 2 packs/day (480 mL) during the 28-day intervention period (14 days before surgery and 14 days after surgery) in addition to a normal diet (or in lieu of part of a normal diet) (n = 14, but 13 analysed) **Comparator group:** no intervention (n = 14) **Use of additional interventions:** none stated
Outcomes	**Primary outcome:** Postoperative nutritional status (weight, lean body mass, albumin, prealbumin) **Secondary outcomes:** Inflammatory marker levels (CRP, IL6, white blood cell count, body temperature), compliance with the Prosure® dosage and the occurrence of postoperative complications

Hanai 2018 (*Continued*)

Funding sources	None declared
Declarations of interest	None declared
Notes	**Participants lost to follow-up:** Quote: "For the intent-to-treat analysis, the object of the analysis included the registered subjects in each arm." NB: according to the CONSORT diagram in the manuscript, one person in the intervention group was, quote: "Excluded due to incomplete data", to give a sample size for analysis of 13 **Other:** Quote: "nine subjects in each arm would be required to detect a statistically significant difference by Student's t-test [α = 0.1 (bilateral), 1 − β = 0.8]."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No statement on the generation of the random sequence
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No statement on blinding, but we presumed non-blinded as the intervention group received sachets and the control group received no intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding or who outcome assessors were
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence from the published data Quote: "For the intent-to-treat analysis, the object of the analysis included the registered subjects in each arm" NB: 1 patient randomised to the intervention group was, quote: "Excluded due to incomplete data"
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	No evidence from the published data

AA: (EPA+DHA)/arachidonic acid ratio
ASEPSIS: **A**dditional treatment, **S**erous discharge, **E**rythema, **P**urulent exudate, **S**eparation of deep tissues, **I**solation of bacteria, **S**tay duration as inpatient
COOP-WONCA: Dartmouth-Northern New England Primary Care Cooperative Information Project-World Organization of National Colleges, Academies and Academic Associations of general Practitioners
CRP: C-reactive protein

DHA: docosahexaenoic acid
ENT: ear, nose and throat
EORTC: European Organisation for Research and Treatment of Cancer
EPA: eicosapentaenoic acid
ICU: intensive care unit
IQR: interquartile range
IL-10: interleukin 10
ITT: intention-to-treat
i.v.: intravenous
NG: nasogastric
PEG: percutaneous endoscopic gastrostomy
POD: postoperative day
QOL: quality of life
RNA: ribonucleic acid
SD: standard deviation
STD: standard group
TLC: total lymphocyte count

Characteristics of excluded studies *[ordered by year of study]*

Study	Reason for exclusion
Linn 1988	**Allocation:** not randomised
De Luis 2005a	**Allocation:** randomised **Participants:** post hospital discharge after head and neck surgery **Interventions:** immunonutrition only (no standard diet comparison)
Buijs 2010	**Allocation:** randomised **Participants:** head and neck cancer patients who were malnourished **Interventions:** standard feed or standard feed plus immunonutrition perioperatively **Outcomes:** patients and outcome data included in another trial
De Luis 2010	**Allocation:** randomised **Participants:** head and neck cancer patients **Interventions:** 2 doses of arginine (high and medium)
De Luis 2013	**Allocation:** not randomised
De Luis 2015	**Allocation:** randomised **Participants:** head and neck cancer patients **Interventions:** 3 different doses of arginine (low, medium, high) but no standard polymeric feed as a comparison
Palma-Milla 2016	**Allocation:** randomised **Participants:** head and neck cancer patients **Interventions:** "new immunomodulatory formula or that commonly used in clinical practice" (i.e. both groups received immunonutrition)

(*Continued*)

Reis 2016	**Allocation:** not randomised (systematic review - not head and neck cancer patients)

Characteristics of ongoing studies *[ordered by study ID]*

NCT03261180

Trial name or title	'Nestle Impact Advanced Recovery in improving surgery recovery in patients with head and neck cancer (official title "Perioperative nutritional optimization in head and neck cancer patients")
Methods	Non-blinded, parallel-group randomised controlled trial with 5 days pre- and 5 days postoperative duration of treatment and 30 days duration of follow-up
Participants	**Sample size:** 330 participants **Inclusion criteria:** Quote: • "Members of all races and ethnic groups will be included • Patients must be diagnosed with cancer of the head and neck and must be surgical candidates • Patients must be indicated for major head and neck surgery, defined as surgeries with an anticipated post-surgical hospital stay of 4 or more days; examples of major surgeries include, but are not limited to, total laryngectomy, large oral cavity, oropharyngeal, salivary gland, or soft tissue resections requiring free flap or major regional flap (e.g. pectoralis major flap), and large skull base procedures requiring extensive skull base reconstruction • Patients must have cross-sectional body imaging (positron emission tomography [PET]-computed tomography [CT] or equivalent) performed within 4 weeks of study enrollment and available for review • Patient must be willing to receive Nestle IMPACT Advance Recovery for five days prior to planned surgery as well as for 5 days after surgery • Ability to understand and the willingness to sign a written informed consent document" **Exclusion criteria:** Quote: • "Patients with known distant metastases or other malignancies • Patients unable to tolerate oral intake by mouth or per enteral feeding tube • Patients with galactosemia • Patients who have received any investigational medication within 6 weeks of enrollment, or who are scheduled to receive an investigational drug during the course of the study • Patients currently taking IMPACT or other immunonutrition products (arginine-containing supplements) will be excluded; other forms of nutritional supplementation, such as caloric supplementation, tube feeding, or other dietary supplements are allowed on study • Patients currently taking anabolic steroids will be excluded; patients taking corticosteroids are allowed on study • Psychiatric illness/social situations that would limit compliance with study requirements • Excluded patients will be allowed to participate in the trial on an observational basis only"
Interventions	**Intervention group:** Nestlé Impact AR (Group I). Patients receive Nestlé Impact AR for 5 days before and after surgery in addition to regular diet **Comparator group:** regular diet (Group II). Patients receive regular diet.

NCT03261180 (*Continued*)

Outcomes	**Primary outcome:** Quote: "Primary: Rate of post-operative wound complications" (within 30 days after major head and neck surgery) **Secondary outcomes:** Rate of other postoperative complications (within 30 days after surgery) and sarcopenia (within 30 days after major head and neck surgery) **Other:** Sarcopenia-related gene expression (up to 30 days post-surgery)
Starting date	Estimated: 30 April 2018
Contact information	Daniel R. Clayburgh (503-494-5355), OHSU Knight Cancer Institute
Notes	Study not yet recruiting (https://clinicaltrials.gov/ct2/show/NCT03261180 accessed 9 May 2018)

DATA AND ANALYSES

Comparison 1. Immunonutrition versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative length of hospital stay	10	757	Mean Difference (IV, Random, 95% CI)	-2.50 [-5.11, 0.12]
1.1 Pre-operative and postoperative feeding	4	403	Mean Difference (IV, Random, 95% CI)	-0.30 [-2.82, 2.21]
1.2 Postoperative feeding only	6	354	Mean Difference (IV, Random, 95% CI)	-4.47 [-8.46, -0.48]
2 Wound infection	12	812	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.70, 1.26]
2.1 Pre-operative and postoperative feeding	6	458	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.72, 1.33]
2.2 Postoperative feeding only	6	354	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.19, 1.59]
3 Fistula formation	10	747	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.27, 0.85]
3.1 Pre-operative and postoperative feeding	4	393	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.33, 1.62]
3.2 Postoperative feeding only	6	354	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.14, 0.71]
4 Adverse events	9	719	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.86, 2.06]
4.1 Pre-operative and postoperative feeding	2	325	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.30, 2.50]
4.2 Postoperative feeding only	7	394	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.82, 2.46]
5 All-cause mortality	14	776	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.48, 3.66]
5.1 Pre-operative and postoperative feeding	6	357	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.28, 4.60]
5.2 Postoperative feeding only	8	419	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.29, 8.53]

Analysis 1.1. Comparison 1 Immunonutrition versus standard care, Outcome 1 Postoperative length of hospital stay.

Review: Immunonutrition for patients undergoing surgery for head and neck cancer

Comparison: 1 Immunonutrition versus standard care

Outcome: 1 Postoperative length of hospital stay

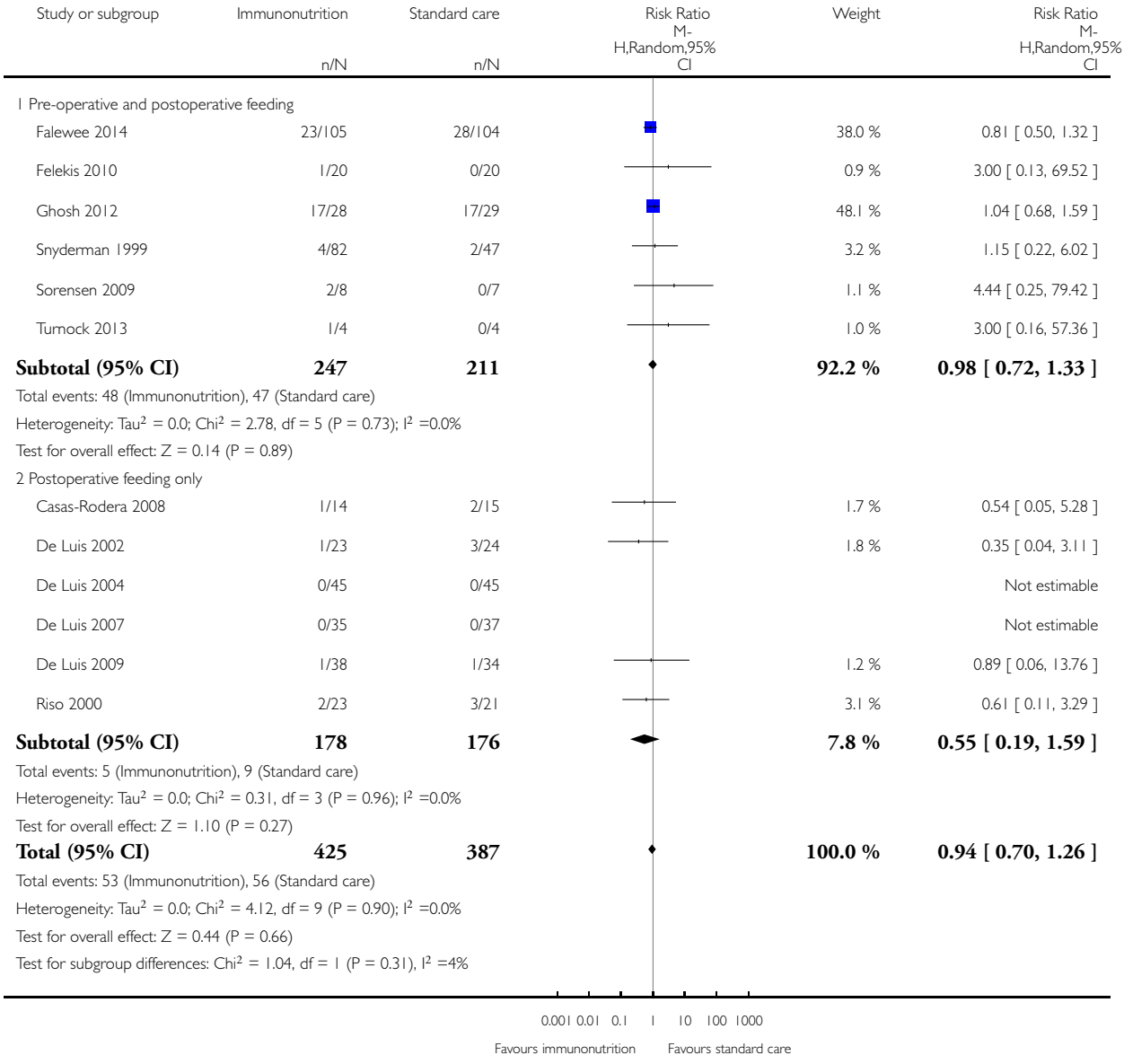
Study or subgroup	Immunonutrition N	Mean(SD)[days]	Standard care N	Mean(SD)[days]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Pre-operative and postoperative feeding							
Snyderman 1999	82	15.3 (9.1)	47	17.4 (11.9)		20.1 %	-2.10 [-6.03, 1.83]
Ghosh 2012	28	31.1 (20.52)	29	35.3 (32.61)		3.1 %	-4.20 [-18.29, 9.89]
Turnock 2013	4	18 (16.7)	4	18.5 (7.7)		2.0 %	-0.50 [-18.52, 17.52]
Falewee 2014	105	23.6 (13.7)	104	22.3 (11.5)		22.6 %	1.30 [-2.13, 4.73]
Subtotal (95% CI)	**219**		**184**			**47.8 %**	**-0.30 [-2.82, 2.21]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.94$, df = 3 (P = 0.59); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.24 (P = 0.81)							
2 Postoperative feeding only							
Riso 2000	23	25 (11.6)	21	28 (12.6)		9.8 %	-3.00 [-10.18, 4.18]
De Luis 2002	23	22.8 (11.5)	24	31.2 (19.1)		6.9 %	-8.40 [-17.37, 0.57]
De Luis 2004	45	25.8 (15)	45	35 (24.6)		7.6 %	-9.20 [-17.62, -0.78]
De Luis 2007	35	27.9 (21)	37	28.2 (12)		8.4 %	-0.30 [-8.26, 7.66]
Casas-Rodera 2008	14	18.57 (7.75)	15	18.27 (7.51)		13.8 %	0.30 [-5.26, 5.86]
De Luis 2009	38	24.3 (14)	34	36.1 (27)		5.7 %	-11.80 [-21.91, -1.69]
Subtotal (95% CI)	**178**		**176**			**52.2 %**	**-4.47 [-8.46, -0.48]**
Heterogeneity: $Tau^2 = 8.96$; $Chi^2 = 7.87$, df = 5 (P = 0.16); $I^2 = 36\%$							
Test for overall effect: Z = 2.19 (P = 0.028)							
Total (95% CI)	**397**		**360**			**100.0 %**	**-2.50 [-5.11, 0.12]**
Heterogeneity: $Tau^2 = 4.82$; $Chi^2 = 12.89$, df = 9 (P = 0.17); $I^2 = 30\%$							
Test for overall effect: Z = 1.87 (P = 0.061)							
Test for subgroup differences: $Chi^2 = 2.99$, df = 1 (P = 0.08), $I^2 = 67\%$							

Analysis 1.2. Comparison 1 Immunonutrition versus standard care, Outcome 2 Wound infection.

Review: Immunonutrition for patients undergoing surgery for head and neck cancer

Comparison: 1 Immunonutrition versus standard care

Outcome: 2 Wound infection

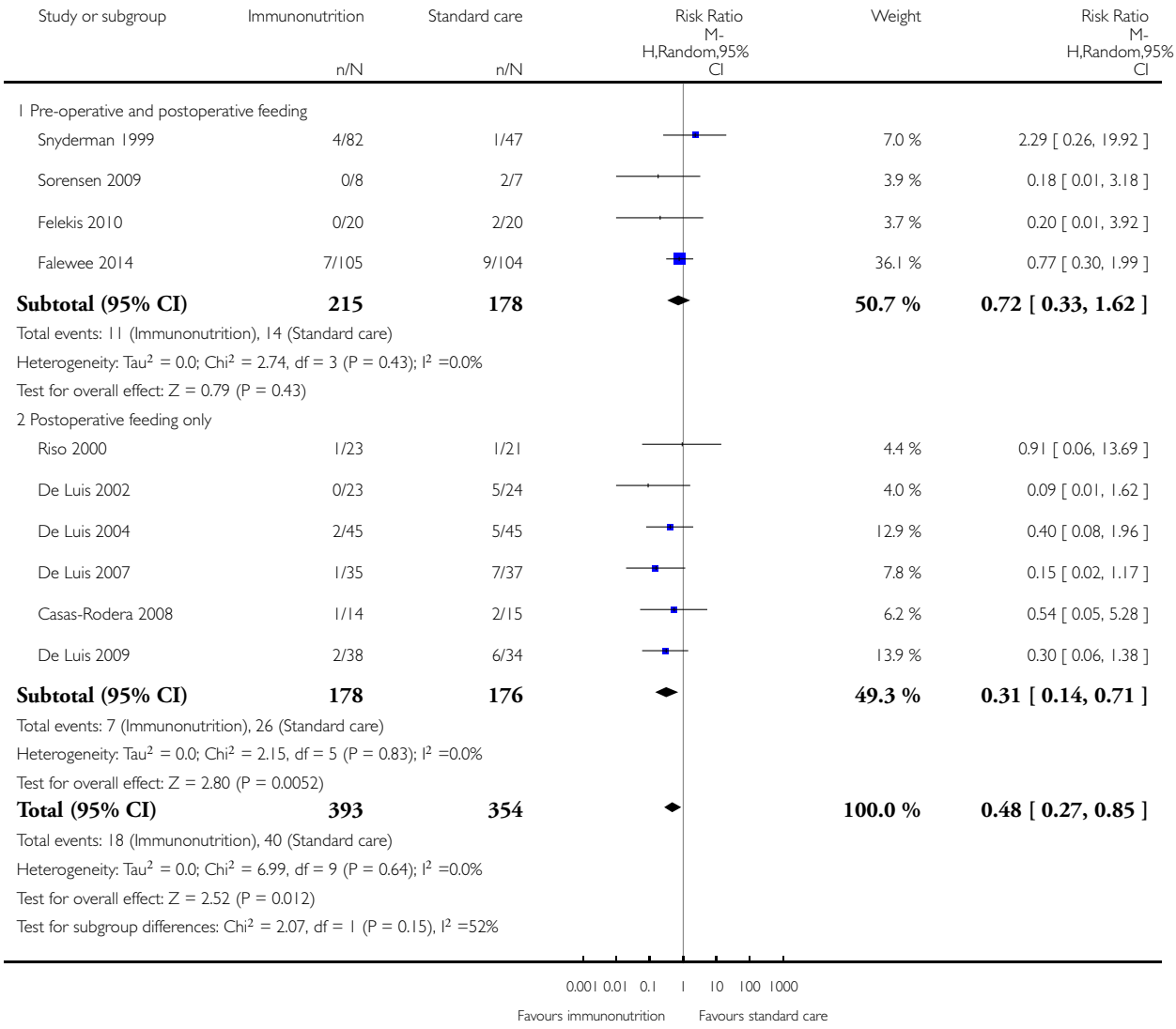


Analysis 1.3. Comparison 1 Immunonutrition versus standard care, Outcome 3 Fistula formation.

Review: Immunonutrition for patients undergoing surgery for head and neck cancer

Comparison: 1 Immunonutrition versus standard care

Outcome: 3 Fistula formation

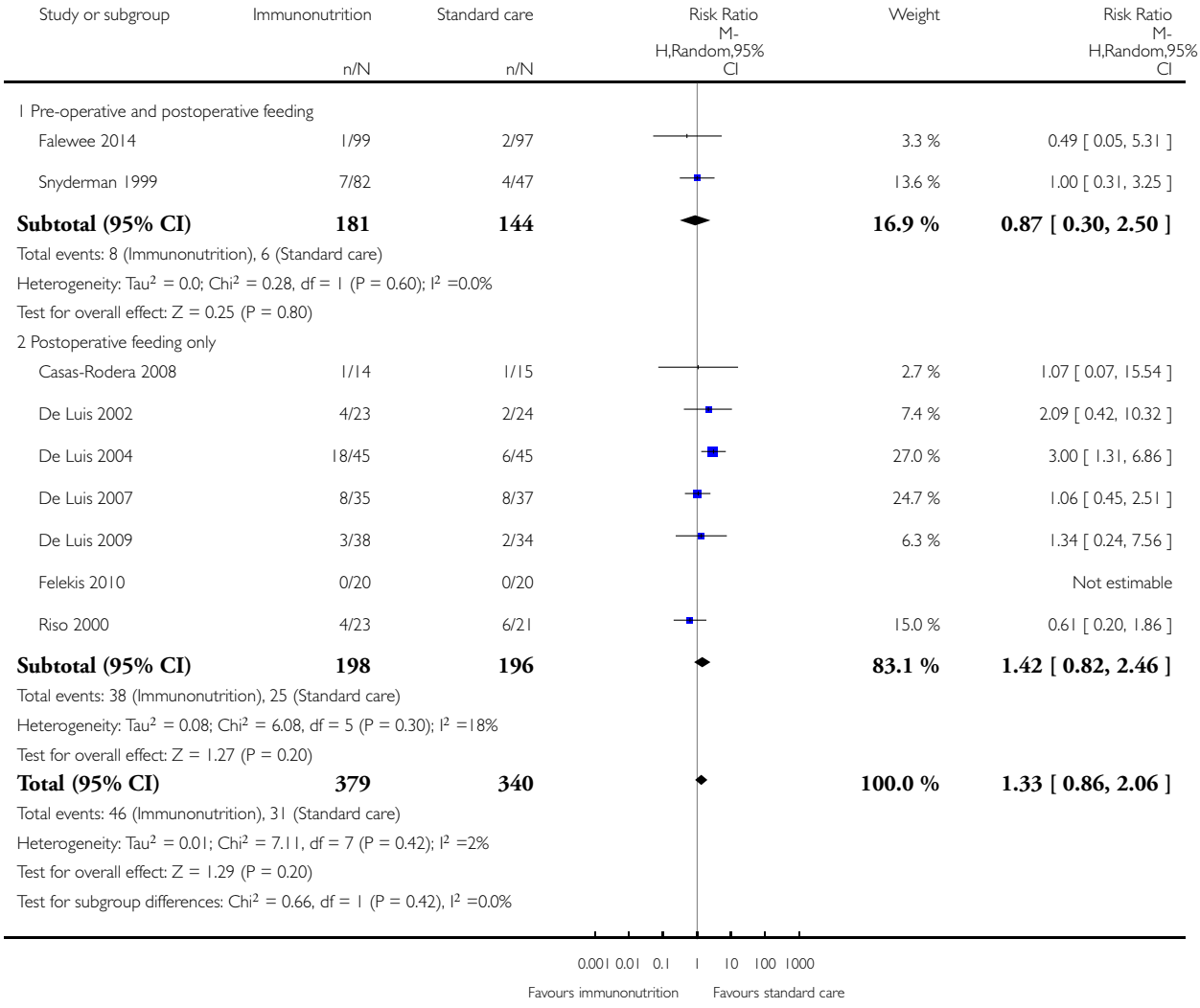


Analysis 1.4. Comparison 1 Immunonutrition versus standard care, Outcome 4 Adverse events.

Review: Immunonutrition for patients undergoing surgery for head and neck cancer

Comparison: 1 Immunonutrition versus standard care

Outcome: 4 Adverse events

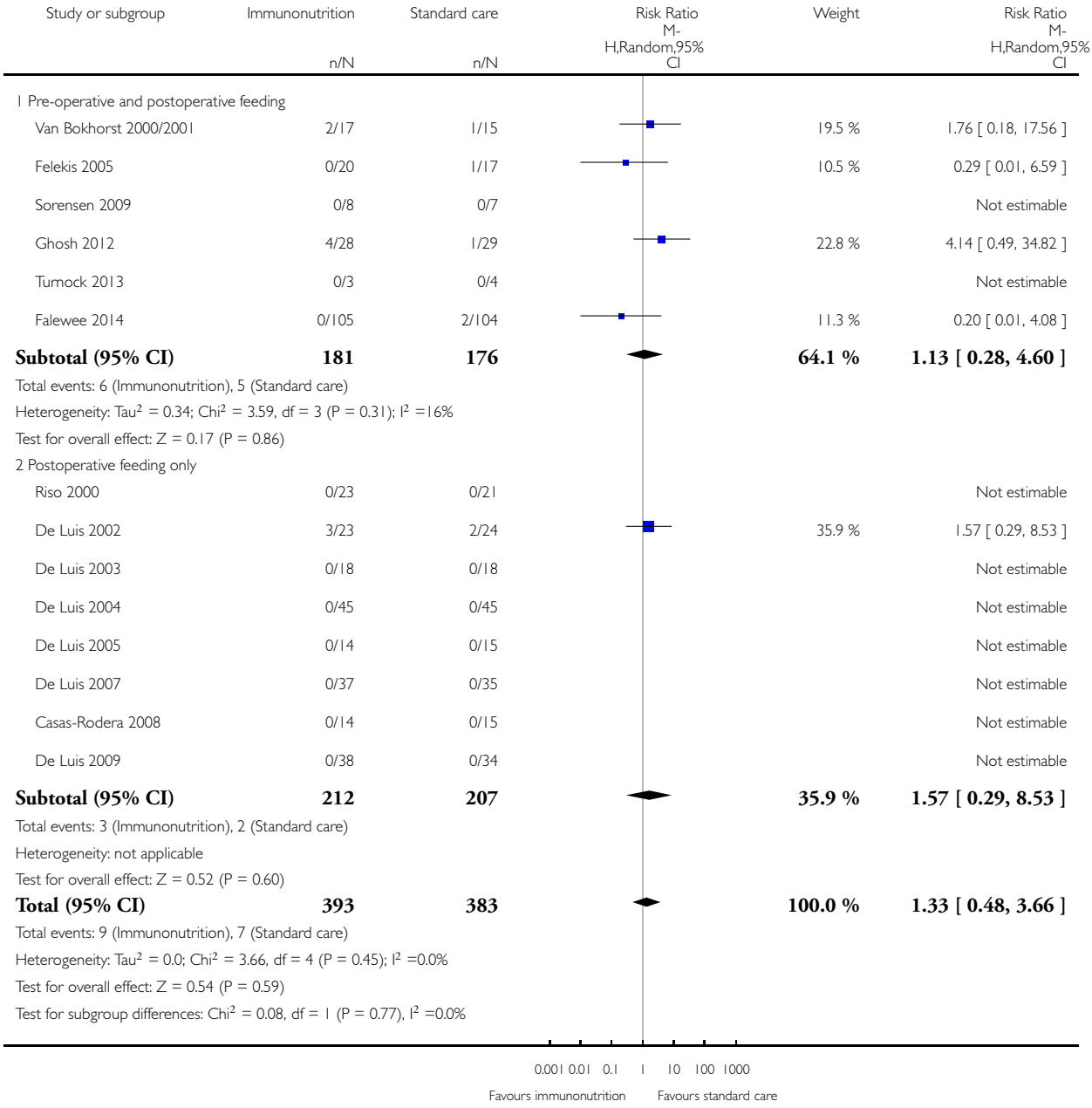


Analysis 1.5. Comparison 1 Immunonutrition versus standard care, Outcome 5 All-cause mortality.

Review: Immunonutrition for patients undergoing surgery for head and neck cancer

Comparison: 1 Immunonutrition versus standard care

Outcome: 5 All-cause mortality



ADDITIONAL TABLES

Table 1. Interventions

						Duration of supplements		
Study	**Groups**	**Control**	**Active**	**Isocaloric/ isonitrogenous**	**Target energy intake**	**Pre-operation**	**Post-operation**	**Length of follow-up**
Snyderman 1999	1. Active pre- and postoperative 2. Active postoperative only 3. Control pre- and postoperative 4. Control postoperative only	Polymeric (Replete, Resource, Isosource, Jevity, Vivonex, Osmolite)	Polymeric + arginine (Impact)	Not stated	500 mL per day pre-operation (500 kcal) 1000 mL per day postoperation (1000 kcal)	≥ 5 days	≥ 7 days	1 month postoperation
Riso 2000	1. Active postoperative enteral 2. Control postoperative enteral Both groups received parenteral nutrition for 3 days postoperatively to achieve nutritional goal	Polymeric (Nutrison protein plus)	Polymeric + arginine (Nutrison intensive)	Yes	31 kcal/kg per day by POD4	None	≥ 10 following total laryngectomy, ≥ 21 days following partial laryngectomy	To hospital discharge
Van Bokhorst 2000/2001	1. No preoperative nutritional support + postoperative standard formula 2. Pre-operative + postoperative standard	Polymeric	Polymeric + arginine ("41% of casein proteins were replaced by arginine")	Yes	150% of basal requirement	7 to 10 days	≥ 10 days	7 days postoperation and greater than or equal to 16 months (survival)

Table 1. Interventions (*Continued*)

	formula 3. Arginine supplemented pre- and postoperative							
De Luis 2002	1. Postoperative supplement with arginine + fibre 2. Postoperative polymeric control	Polymeric	Polymeric + arginine (0.625 g/100 mL) + fibre (0.9 g/100 mL) (NB control and active formulas contained the same ratio of ω6:ω3 fats)	Yes	32 kcal/kg per day by POD4	None	Average duration 22 days (± 12 days) across groups	14 days postoperatively, and 3 months post hospital discharge (mortality)
De Luis 2003	1. Postoperative enteral supplement with arginine + fibre 2. Postoperative polymeric control	Polymeric	Polymeric + arginine (0.625 g/100 mL) + fibre (0.9 g/100 mL) (NB control and active formulas contained the same ratio of ω6:ω3 fats)	Yes	32 kcal/kg per day by POD4	None	Average duration 20 days in group 1	5 days post-operation
De Luis 2004	1. Postoperative polymeric + arginine + fibre 2. Postoperative polymeric control + fibre	Polymeric + fibre (0.9 g/100 mL)	Polymeric + arginine (0.625 g/100 mL) + fibre (0.9 g/100 mL) (NB control and active formulas contained the same ratio of ω6:ω3 fats)	Yes	32 kcal/kg per day by POD4	None	$\geq$ 10 days	Day 14

Table 1. Interventions (*Continued*)

De Luis 2005	1. Postoperative polymeric + arginine 2. Postoperative polymeric control	Polymeric + fibre (0.9 g/100 mL)	Polymeric + arginine (12.5 g/day) + fibre (0.9 g/100 mL)	Yes	Not stated	None	Average duration 20 days in group 1	6 days post-operation
Felekis 2005	1. Active pre- and postoperative 2. Regular oral diet and standard polymeric enteral feeding pre- and postoperatively	Polymeric	Undefined enteral immunonutrition	Yes	Not stated	6 days	8 days	Not stated
De Luis 2007	1. Postoperative polymeric + arginine 2. Postoperative polymeric control	Polymeric + fibre (0.9 g/100 mL)	Polymeric + arginine (0.85 g/100 mL) + fibre (0.9 g/100 mL) (NB control and active formulas contained the same ratio of ω6:ω3 fats)	Yes	32 kcal/kg per day by POD4	None	$\geq$ 10 days	12 days post-operation
Casas-Rodera 2008	1. Postoperative arginine enhanced formula 2. Polymeric control 3. Postoperative arginine enhanced formula RNA and omega-	Group 2 polymeric	Group 1 arginine-enhanced formula (NB data from Group 1 not used in analyses) Group 3 arginine (1.3 g/100 mL), RNA (0.12	No (control 122 kcal/100 mL, active 101 kcal/100 mL)	Requirements (used Harris Benedict formula with a stress factor correction of 1.4) by POD3	None	Average duration of 14.5 ± 8 days	14 days post-surgery

Table 1. Interventions (*Continued*)

	3 fatty acids		g/100 mL) and ratio of ω6:ω3 fats noted as "0.7 g"					
De Luis 2009	1. Active postoperative (arginine) + fibre 2. Control postoperative (standard enteral nutrition)	Polymeric	Polymeric + arginine (0.85 g/100 mL) + fibre (0.9 g/100 mL) (NB control and active formulas contained the same ratio of ω6:ω3 fats)	Yes	32 kcal/kg; 1.7 g protein/kg on POD4	None	≥ 10 days	10 days post-operation
Sorensen 2009	1. Active pre- and postoperative (arginine, glutamine, nucleotides and omega-3 enriched) 2. Control pre- and postoperative (standard enteral nutrition)	Isosource	Polymeric + arginine and glutamine (Impact Recover (oral drink, containing 16.3 g arginine, 20 g glutamine, 1.6 g nucleotides, and 1.7 g ω3 fatty acids/L) or Impact glutamine (tube feed, containing 16.3 g arginine, 15 g glutamine, 1.6 g nucleotides and 2.7 g ω3 fatty acids/L))	No (Impact Recover = 960 kcal/L; Impact glutamine = 1300 kcal/L; Isosource = 1440 kcal/L)	~1 L per day pre-operatively, at least 1 L per day postoperatively (~50% to 60% of basal requirements from intervention)	7 days	7 days	29 days post-operation
Felekis 2010	1. Control pre-	Polymeric (Nu-	Polymeric + ω3 fatty	Yes	Requirement (based	5 days	8 days	8 days post-operation

Table 1. Interventions (*Continued*)

	and postoperative 2. Active pre- and postoperative	trison, Nutricia)	acids, arginine, RNA (Impact, Novartis)		on Harris and Benedict equations) by POD4			
Ghosh 2012	1. Control pre- and postoperative 2. Active pre- and postoperative	Polymeric	Polymeric + ω3 fatty acids (1.7 g/L), arginine (1.25 g/L), RNA (1.2 g/L) (Impact)	Yes	Nutritional requirements based on Schofield calculation, 500 mL/day pre-operatively, 1000 mL/day postoperatively (also allowed to eat and drink if able). Any calorific shortfall was made up using standard proprietary feeds	5 days	7 days	30 days post-operation
Turnock 2013	1. Control - no supplements pre-operation, postoperative standard supplements 2. Active - pre- (oral) and postoperative (enteral then oral to day 5) supplements	Isosource standard (postoperative only)	Polymeric + ω3 fatty acids (3.3 and 1.7 g/L EPA and DHA for oral and enteral products, respectively), arginine (12.6 and 12.5 g/L for oral and enteral products), RNA (1.3 and 1.2 g/L for oral and enteral products) (Impact)	No (oral/enteral Impact 1000 kcal/L; Isosource standard 1200 kcal/L)	Requirements (25 to 30 kcal/kg)	5 days	$\geq$ 5 days	Hospital discharge

Table 1. Interventions (*Continued*)

De Luis 2014	1. Active post-operative 2. Control postoperative	Polymeric	Polymeric + arginine (8 g/L, 20 g/day) (NB control and active formulas contained the same ratio of $\omega 6$:$\omega 3$ fats and the same amount of fibre 13.8 g/L)	No (control 1.118 kcal/L, active 1.020 kcal/L)	Requirements (35 kcal/kg, 1.7 g protein/kg)	None	Minimal of 15 days	10 days post-surgery
Falewee 2014	1. Pre- and postoperative control 2. Preoperative active, postoperative control 3. Pre- and postoperative active	Impact without immunonutrients	Polymeric + $\omega 3$ fatty acids (1.0 g per sachet (oral) and 1.65 g/500 mL (enteral)), arginine (3.8 g per sachet (oral) and 6.5 g/500 mL (enteral)), RNA (0.45 g per sachet (oral) and 0.65 g/500 mL (enteral)) (Oral Impact preoperatively and Enteral Impact postoperatively)	Yes	Requirements (calculated using SFNEP French recommendations)	7 days	7 to 15 days	90 days post-surgery
Azman 2015	1. Postoperative active 2. Postoperative no intervention	None	Glutamine powder (30 g/day) (Glutamine Plus, Fresenius Kabi)	No control intervention	30 to 40 kcal/kg/day	None	4 weeks	4 weeks post-operation

Table 1. Interventions (*Continued*)

Hanai 2018	1. Pre- and postoperative active 2. Pre-and post-operative no intervention	None	Prosure (an eicosapentaenoic acid (EPA) enriched oral nutritional supplement) at a dose of 2 packs per day (480 mL)	No control intervention	Prosure was administered in addition to a normal diet (or in lieu of part of a normal diet). Quote: "The dietary intake was not limited"	14 days	14 days	14 days post-operation

DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
POD: postoperative day
RNA: ribonucleic acid
SFNEP: Société Francophone de Nutrition Entérale et Parentérale

Table 2. Baseline patient characteristics

	Number		Mean age		Sex M:F		Mean weight (kg)		BMI	
Study	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**
Snyderman 1999	47	82	61	63	32:15	63:19	67	71	Not reported	Not reported
Riso 2000	21	23	63	61	18:3	21:2	66	64	23.2	22.1
Van Bokhorst 2000/2001	15	17	60	59	7:8	12:5	55	62	Not reported	Not reported
De Luis 2002	24	23	59	63	3:21	2:21	68	68	24.1	26.2
De Luis 2003	18	18	59	63	1:27	1:17	69	69	24.1	26.2
De Luis 2004	45	45	61	60	3:42	3:42	69	70	25.1	25.2

Table 2. Baseline patient characteristics (*Continued*)

De Luis 2005	15	14	63	61	3:12	2:12	Not reported	Not reported	24.1	24.6
Felekis 2005	17	20	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
De Luis 2007	37	35	62	62	3:34	4:31	69	68	25.1	24.0
Casas-Rodera 2008*	15	14	54	50	15:0	14:0	66	68	Not reported	Not reported
De Luis 2009	34	38	61	63	27:7	30:8	71	73	26.4	26.5
Sorensen 2009	7	8	59	62	7:0	8:0	69	71	22.3	22.7
Felekis 2010	20	20	63	61	18:2	18:2	Not reported	Not reported	Not reported	Not reported
Ghosh 2012**	29	28	60	62	26:3	24:4	65	72	24	26
Turnock 2013	4	4	47	51	3:1	3:1	67	67	Not reported	Not reported
De Luis 2014	40	42	63.6	65.5	35:5	37:5	70	72	25.1	25.7
Falewee 2014***	104	105	59	59	86:18	87:18	69	70	23.7	23.6
Azman 2015****	22	22	Not reported	Not reported	15:7	9:13	Not reported	Not reported	Not reported	Not reported
Hanai 2018	14	13	66.1	61.5	8:6	8:5	Not reported	Not reported	Not reported	Not reported

* Two different values for weight reported in manuscript: data from Table II in manuscript are reported here.
** Data reported in manuscript (and here) as median values for age, weight and body mass index (BMI).
*** Additional data supplied by authors.
**** Median age across both treatment groups was 49 years (range 22 to 74 years). No data by treatment group available.

Table 3. Methodological quality of trials

Study	Generation of allocation sequence	Allocation concealment	Power calculations	Patients blinded	Assessors blinded	Analysed as intention-to-treat (ITT)
Snyderman 1999	Tables	Not stated	Not stated	Unclear which treatment groups were blinded	Unclear which treatment groups were blinded	Yes - stated ITT
Riso 2000	Computer-generated*	Sealed envelopes* (not defined as opaque)	Not done*	Stated "double-blindly performed" but no indication as to who was blinded*	Stated "double-blindly performed" but no indication as to who was blinded*	Yes - no attrition according to number of participants included in analyses
Van Bokhorst 2000/2001	Computer-generated	Not stated	Yes	Yes**	Yes**	Yes - no attrition according to number of participants included in analyses for relevant outcomes
De Luis 2002	Tables*	Sealed envelopes* (not defined as opaque)	Yes	Yes	Yes	Yes - stated "Any drop-outs were present in the study"
De Luis 2003	Tables*	Sealed envelopes (not defined as opaque)	Yes*	Yes	Yes	Yes - stated ITT
De Luis 2004	Tables*	Sealed envelopes* (not defined as opaque)	Yes	States blinded, but no indication as to who was blinded*	States blinded, but no indication as to who was blinded*	Yes - stated ITT
De Luis 2005	Tables*	Sealed envelopes (not defined as opaque)	Yes*	Stated "Study was blinded" but no indication as to who was blinded	Stated "Study was blinded" but no indication as to who was blinded	Yes - stated ITT
Felekis 2005	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
De Luis 2007	Tables*	Envelopes* (not defined as opaque)	Yes	States blinded, but no indication as to who	States blinded, but no indica-	Yes - stated ITT

Table 3. Methodological quality of trials (*Continued*)

				was blinded*	tion as to who was blinded*	
Casas-Rodera 2008	Stated "randomly allocated" but no information on how sequence was generated	Not stated	Not stated	Not stated	Not stated	Yes - stated "no dropouts were present in the study"
De Luis 2009	Stated "randomly allocated" but no information on how sequence was generated	Not stated	Yes	Yes	Yes	Yes - stated ITT
Sorensen 2009	Stated as a "randomized design" but no information on how sequence was generated	Envelopes (not defined as opaque)	Not done	Partial	Partial	Unclear - no statement on dropouts
Felekis 2010	Stated "randomization generator"	Not clear	Not done*	Stated "double blinded" but no indication as to who was blinded	Stated "double blinded" but no indication as to who was blinded	Yes - no loss to follow-up described and stated "no dropouts occurred due to intolerance"
Ghosh 2012	"Randomisation lists" (pharmacy clinical trials unit)	Pharmacy (central telephone assignment)	Yes	Yes	Yes	Yes - stated ITT
Turnock 2013	Computer-generated	Opaque, sealed envelopes	Pilot study	No	No	Yes - no attrition according to number of participants included in analyses
De Luis 2014	Not stated	Not stated	Not stated	Yes	Yes	Yes - no attrition
Falewee 2014	Computer-generated	Pharmacy clinical trials unit	Yes	Yes	Yes	Yes*

Table 3. Methodological quality of trials (*Continued*)

Azman 2015	Random ballot picking	Sealed envelopes (not defined as opaque)	Yes	No	No	Yes
Hanai 2018	Not stated	Not stated	Yes	Not stated, but assumed non-blinded as intervention group received sachets and control group received no intervention	Not stated	Yes - stated ITT (NB: 1 patient, quote "Excluded due to incomplete data")

* Additional information provided by authors.
** Groups 2 and 3 included in analyses; authors stated that these groups were blinded.

Table 4. Other complications

	Number		Other complications definition	Other complications - total		Pneumonia		Urinary tract	
Study	**Control**	**Intervention**		**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**
Pre- and postoperative feeding									
Snyderman 1999	47	82	"...infectious complications were judged using CDC criteria and were considered significant if antibiotic therapy was instituted" (NB: total for other complications provided here	19	19	-	-	-	-

Table 4. Other complications (*Continued*)

			include "postoperative infection" but**not** "wound healing problem" or "fistula")						
Van Bokhorst 2000/ 2001	15	17	"Postoperative complications were categorized as absent, minor (including minor wound infections, redness and induration of the wound, pulmonary infections, and urinary tract infections), or major (including wound infections requiring surgical drainage, orocutaneous or pharyngocutaneous fistula, flap failure, radiologic signs of anastomotic leakage,	7 major	10 major	-	-	-	-

Table 4. Other complications (*Continued*)

			respiratory insufficiency, cardiac failure, and septic shock)" (NB: data on individual complications not given in manuscript so the total for other complications provided here **may include** fistula and wound infection)						
Felekis 2005	17	20	Reported as major and minor, but otherwise not defined	9 (6 major, 3 minor)	4 (2 major, 2 minor)	-	-	-	-
Sorensen 2009	7	8	"Serious wound complications were recorded as they occurred and included wound infection, wound dehiscence, and wound fistula. Wound assessments using the	2 (0 major 2 minor)	5 (1 major - wound dehiscence; 4 minor)	-	-	-	-

Table 4. Other complications (*Continued*)

			ASEPSIS scoring method were performed daily and photographic images were taken on several postoperative days." Authors also noted that "Patients may have had more than one complication" (NB: figures provided here include "wound dehiscence" (classed as major) and "other" (urinary tract infection and nosocomial pneumonia combined as one group) (classed as minor) **but exclude** "wound fistula" and "wound infection").						

Table 4. Other complications (*Continued*)

Felekis 2010	20	20	Minor described in results as "a slight increase of the temperature (< 38°), without an identifiable source of infection". Major described in results as including pneumonia, urinary tract infection, fistula and wound infection. NB: figures provided here **do not** include fistula and wound infection.	6 (3 minor, 3 major - 2 pneumonia, 1 UTI)	2 (2 minor, 0 major)	2	0	1	0
Ghosh 2012	29	28	"The primary outcome event was defined as any patient with an infection of the lower respiratory tract, gastrointestinal tract, urinary tract	8 with chest, urinary, gastrointestinal or blood infection 17 with neck, primary site, donor site, or PEG site infection	12 with chest, urinary, gastrointestinal or blood infection 17 with neck, primary site, donor site, or PEG site infection	4	9	1	2

Table 4. Other complications (*Continued*)

			or blood which required antibiotic treatment and occurred at any time, up to the 30th postoperative day." "Secondary outcome measures included infections of primary surgical site, neck wound, PEG site, tracheostomy, free-flap or split skin graft donor site." "...the surgical site/wound infections were defined according to CDC Definitions of Nosocomial Surgical Site infections, 1992 and the ASEPSIS wound						

Table 4. Other complications (*Continued*)

			score. The diagnosis of the non-wound infection was as stipulated in the Trial Antibiotic Policy, which also governed how any infective complication diagnosed throughout the trial was to be treated. "						
Turnock 2013	4	4	"General infections (urinary tract infection, respiratory tract infection), flap anastomosis complications (venous or arterial), and wound complications (dehiscence, tissue necrosis, haematoma, chyle leak, salivary fistula or wound infection)	2 (infectious)	0	-	-	-	-

Table 4. Other complications (*Continued*)

			were recorded. Infectious complications were judged using CDC criteria and were considered significant if antibiotic therapy was instituted." (NB: figures provided here **do not** include wound infection).						
Falewee 2014*	104	105	Infectious complications: "systemic infection requiring antibiotic treatment (septicaemia, bacteraemia), surgical site infection (according to CDC Definitions of Nosocomial Surgical Site infections), documented	-	-	-	-	-	-

Table 4. Other complications (*Continued*)

			nosocomial pneumopathy, up to the 30th postoperative day." Surgical site infections (SSI) : "primary surgical site, neck wound, free-flap or split skin graft donor site, and tracheotomy"						
Hanai 2018	14	13	Clinical complications presented as numbers of patients with "wound complications" classified according to Clavien-Dindo system	7	4	-	-	-	-
Postoperative feeding only									
Riso 2000	21	23	"Postoperative complications were recorded as none, minor (urinary tract infection; respira-	4 major (1 flap necrosis, 3 purulent drainage) 1 minor (respiratory tract)	2 (purulent drainage)	1 (respiratory tract)	0	0	0

Table 4. Other complications (*Continued*)

			tory tract infection: abnormal chest X-ray), and major (fistula; wound infection; spontaneous or surgical purulent drainage and flap necrosis; anastomotic leakage)." (NB: figures provided here **exclude** reported fistula).						
De Luis 2002	24	23	"Postoperative complications were recorded as none, general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive unfiltra-	4	5	-	-	-	-

Table 4. Other complications (*Continued*)

			tion, temperature above 38.5°C and isolation of pathogens from the sputum or blood culture and/or urinary tract infection was diagnosed if the urine culture showed at least 10^5 colonies of a pathogen) and local complications such as fistula and/or wound infection, assessing all complications using standard methods and the same investigator." (NB: figures provided here **exclude** reported fistula).						
De Luis 2003	18	18	Not collected	-	-	-	-	-	-

Table 4. Other complications (*Continued*)

De Luis 2004	45	45	"Postoperative complications were recorded as none, general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive unfiltration, temperature above 38.5°C and isolation of pathogens from the sputum or blood culture and/or urinary tract infection was diagnosed if the urine culture showed at least 10^5 colonies of a pathogen) and local compli-	4	2	-	-	-	-

Table 4. Other complications (*Continued*)

			cations such as fistula and/or wound infection. All complications were assessed with standard methods by the same investigator. " (NB: figures provided here **exclude** reported fistula).						
De Luis 2005	15	14	Not collected	-	-	-	-	-	-
De Luis 2007	37	35	"Postoperative complications were recorded as none; general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive unfiltration, temperature	2	2	-	-	-	-

Table 4. Other complications (*Continued*)

			above 38. 5°C and isolation of pathogens from the sputum or blood culture and/or urinary tract infection was diagnosed if the urine culture showed at least 10^5 colonies of a pathogen) and wound complications, such as fistula and/or wound infection, assessed all complications with standard methods by the same investigator surgeon. " (NB: figures provided here **exclude** reported fistula).						
Casas-Rodera 2008	15	14	"Postoperative complications were recorded as none,	1	0	1	0	0	0

Table 4. Other complications (*Continued*)

			general infections (respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive unfiltration, temperature above 38.5°C and isolation of pathogens from the sputum or blood culture and/or urinary tract infection was diagnosed if the urine culture showed at least 10^5 colonies of a pathogen), and wound complications such as fistula and/or wound infection. All complications						

Table 4. Other complications (*Continued*)

			were assessed with standard methods by the same investigator." (NB: figures provided here **exclude** reported fistula and wound infection).						
De Luis 2009	34	38	"Postoperative complications were registered as none, general infections (urinary tract infection was diagnosed if the urine culture showed at least 10^5 colonies of a pathogen and/or respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive unfiltra-	8	9	-	-	-	-

Table 4. Other complications (*Continued*)

			tion, temperature above 38.5°C and isolation of pathogens from the sputum or blood culture) and local complications such as fistula and/or wound infection, assessed all complications with standard methods by the same investigator." (NB: figures provided here **exclude** reported fistula and wound infection).						
De Luis 2014	40	42	No clinical complications recorded	-	-	-	-	-	-
Azman 2015	22	22	No clinical complications recorded	-	-	-	-	-	-

* Additional data supplied by authors for intention-to-treat (ITT) analysis to be conducted; as such, total n differs from that in the published manuscript.

ASEPSIS: **A**dditional treatment, **S**erous discharge, **E**rythema, **P**urulent exudate, **S**eparation of deep tissues, **I**solation of bacteria, **S**tay duration as inpatient

CDC: Centers for Disease Control and Prevention

PEG: percutaneous endoscopic gastrostomy

UTI: urinary tract infection

APPENDICES

Appendix 1. Search strategies

CENTRAL (via Cochrane Register of Studies)	PubMed	EMBASE (Ovid)
#1 MESH DESCRIPTOR Head and Neck Neoplasms EXPLODE ALL TREES WITH QUALIFIERS SU #2 MESH DESCRIPTOR Otorhinolaryngologic Neoplasms EXPLODE ALL TREES WITH QUALIFIERS SU #3 MESH DESCRIPTOR Otorhinolaryngologic Neoplasms EXPLODE ALL TREES #4 MESH DESCRIPTOR Head and Neck Neoplasms EXPLODE ALL TREES #5 (head near neck):TI,AB,KY #6 ((larynx or laryngeal or glottis or glottic or "oral cavity" or nasopharynx or nasopharyngeal or hypopharynx or hypopharyngeal or pharynx or pharyngeal or parapharyngeal or mouth)):TI,AB,KY #7 (face or facial or oesophageal or esophageal or oesophagus or esophagus or thyroid or salivary or paranasal or "aero digestive" or aerodigestive or aero-digestive):TI,AB,KY #8 #5 OR #6 OR #7 #9 ((cancer* or carcinoma* or neoplasm* or tumor* or tumour* or metastas*)):TI,AB,KY #10 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES #11 #9 OR #10 #12 #8 AND #11 #13 #3 OR #4 OR #12 #14 MESH DESCRIPTOR Surgical Procedures, Operative EXPLODE ALL TREES #15 ((surg* or resect* or reconstruct*)):TI,	#1 ("Head and Neck Neoplasms/surgery"[Mesh]) #2 "Otorhinolaryngologic Neoplasms/surgery"[Mesh] #3 ("Head and Neck Neoplasms"[Mesh]) #4 "Otorhinolaryngologic Neoplasms"[Mesh] #5 ("head neck" OR head-neck OR "head and neck" OR head-and-neck[Title/Abstract]) #6 (larynx or laryngeal or glottis or glottic or "oral cavity" or nasopharynx or nasopharyngeal or hypopharynx or hypopharyngeal or pharynx or pharyngeal or parapharyngeal or mouth[Title/Abstract]) #7 (face or facial or oesophageal or esophageal or oesophagus or esophagus or thyroid or salivary or paranasal or "aero digestive" or aerodigestive or aero-digestive[Title/Abstract]) #8 (#5 OR #6 OR #7) #9 (cancer* or carcinoma* or neoplasm* or tumor* or tumour* or metastas*[Title/Abstract]) #10 "Neoplasms"[Mesh] #11 (#9 OR #10) #12 (#8 AND #11) #13 (#3 OR #4 OR #12) #14 "Surgical Procedures, Operative"[Mesh] #15 (surg* or resect* or reconstruct*[Title/Abstract]) #16 (pharyngectomy or laryngopharyngectomy or laryngectomy or mandibulectomy	1 exp "head and neck tumor"/su [Surgery] 2 exp *"head and neck tumor"/ 3 (head adj3 neck).tw. 4 (larynx or laryngeal or glottis or glottic or "oral cavity" or nasopharynx or nasopharyngeal or hypopharynx or hypopharyngeal or pharynx or pharyngeal or parapharyngeal or mouth).tw 5 (face or facial or oesophageal or esophageal or oesophagus or esophagus or thyroid or salivary or paranasal or "aero digestive" or aerodigestive or aero-digestive).tw 6 3 or 4 or 5 7 (cancer* or carcinoma* or neoplasm* or tumor* or tumour* or metastas*).tw 8 exp *neoplasm/ 9 7 or 8 10 6 and 9 11 2 or 10 12 exp surgery/ 13 (surg* or resect* or reconstruct*).tw. 14 (pharyngectomy or laryngopharyngectomy or laryngectomy or mandibulectomy or commando or esophagectomy or oesophagectomy).tw 15 (neck and dissect*).tw. 16 exp neck dissection/ 17 ((free or myocutaneous) and flap).tw. 18 12 or 13 or 14 or 15 or 16 or 17 19 11 and 18 20 1 or 19 21 exp arginine/ 22 exp omega 3 fatty acid/ or exp omega 6

(*Continued*)

AB,KY
#16 ((pharyngectomy or laryngopharyngectomy or laryngectomy or mandibulectomy or commando or esophagectomy or oesophagectomy)):TI,AB,KY
#17 ((neck and dissect*)):TI,AB,KY
#18 MESH DESCRIPTOR Neck Dissection EXPLODE ALL TREES
#19 (((free or myocutaneous) and flap)):TI,AB,KY
#20 #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 #13 AND #20
#22 #1 OR #2 OR #21
#23 MESH DESCRIPTOR Arginine EXPLODE ALL TREES
#24 (immuno or arginine* or glutamine* or nucleotide* or omega-3 or omega3 or omega-6 or omega6 or "ω-3" or nucleoside* or fibre* or fiber* or IMP1000 or IMP500 or immunostimulat* or immunostimulat*):TI,AB,KY
#25 MESH DESCRIPTOR Fatty Acids, Omega-3 EXPLODE ALL TREES
#26 MESH DESCRIPTOR Fatty Acids, Omega-6 EXPLODE ALL TREES
#27 MESH DESCRIPTOR Glutamine EXPLODE ALL TREES
#28 MESH DESCRIPTOR Nucleotides EXPLODE ALL TREES
#29 MESH DESCRIPTOR Dietary Fiber EXPLODE ALL TREES
#30 (Argininosuccinic* or Benzoylarginine* or Homoarginine* or Nitroarginine* or Tosylarginine* or Methylarginine* or NO2Arg or NOARG or L-NMMA or D-NMMA or TAME or Proglumide* or Xylamide* or Xilamide or Milid or PUFA* or "n-3 fatty acid*" or Docosahexaen* or Neuroprostane* or Icosapentaenoic* or Timnodonic or Linoleic* or Linolenic* or Octadecadienoic* or Linoleate* or Linoelaidic or "n-6 fatty acid*" or Eicosapentaenoic or EPA or O-3FA* or O-6FA*):TI,AB,KY
#31 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
#32 (enteral or polymeric* or Parenteral or diet* or feed* or food* or supplement* or commando or esophagectomy or oesophagectomy[Title/Abstract])
#17 (neck and dissect*[Title/Abstract])
#18 "Neck Dissection"[Mesh]
#19 ((free or myocutaneous[Title/Abstract])) AND flap[Title/Abstract]
#20 (#14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#13 AND #20)
#22 (#1 OR #2 OR #21)
#23 "Arginine"[Mesh]
#24 (immuno or arginine* or glutamine* or nucleotide* or omega-3 or omega3 or omega-6 or omega6 or "ω-3" or nucleoside* or fibre* or fiber* or IMP1000 or IMP500 or immunostimulat* or immunostimulat*[Title/Abstract])
#25 ("Fatty Acids, Omega-3"[Mesh] OR "Fatty Acids, Omega-6"[Mesh])
#26 "Glutamine"[Mesh]
#27 "Nucleotides"[Mesh]
#28 "Dietary Fiber"[Mesh]
#29 (Argininosuccinic* or Benzoylarginine* or Homoarginine* or Nitroarginine* or Tosylarginine* or Methylarginine* or NO2Arg or NOARG or L-NMMA or D-NMMA or TAME or Proglumide* or Xylamide* or Xilamide or Milid or PUFA* or "n-3 fatty acid*" or Docosahexaen* or Neuroprostane* or Icosapentaenoic* or Timnodonic or Linoleic* or Linolenic* or Octadecadienoic* or Linoleate* or Linoelaidic or "n-6 fatty acid*" or Eicosapentaenoic or EPA or O-3FA* or O-6FA*[Title/Abstract])
#30 (#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)
#31 (enteral or polymeric* or Parenteral or diet* or feed* or food* or supplement* or nutri* or formul* or tpn or enteric or Nutraceutical* or tube* or pn or SEN or "Ensure Liquid*"[Title/Abstract])
#32 "Nutrition Therapy"[Mesh]
#33 "Nutritional Support"[Mesh]
#34 "Dietary Supplements"[Mesh]
#35 "Food, Formulated"[Mesh]
#36 (#31 OR #32 OR #33 OR #34 OR #35)
fatty acid/
23 exp glutamine/
24 exp nucleotide/
25 exp dietary fiber/
26 (Argininosuccinic* or Benzoylarginine* or Homoarginine* or Nitroarginine* or Tosylarginine* or Methylarginine* or NO2Arg or NOARG or L-NMMA or D-NMMA or TAME or Proglumide* or Xylamide* or Xilamide or Milid or PUFA* or "n-3 fatty acid*" or Docosahexaen* or Neuroprostane* or Icosapentaenoic* or Timnodonic or Linoleic* or Linolenic* or Octadecadienoic* or Linoleate* or Linoelaidic or "n-6 fatty acid*" or Eicosapentaenoic or EPA or O-3FA* or O-6FA*).tw
27 21 or 22 or 23 or 24 or 25 or 26
28 (enteral or polymeric* or Parenteral or diet* or feed* or food* or supplement* or nutri* or formul* or tpn or enteric or Nutraceutical* or tube* or pn or SEN or "Ensure Liquid*").tw
29 diet therapy/ or diet supplementation/ or nutritional support/
30 exp elemental diet/
31 28 or 29 or 30
32 27 and 31
33 (immunonutri* or immunoenhanc* or imn or ied or Pharmaconutri* or immunemodulat* or immunomodulat* or IMEN or immunoenteral or IEEN or ien or immunodiet* or ((immune* or immuno*) adj6 (enhanc* or enrich*)) or immunoenrich* or ief or ieef).tw
34 (isosource or jevity or vivonex or osmolite or nutrison or "oral impact" or replete or alitraQ or immun-aid or optimental or perative or pivot or stresson or immunaid or nutrisource or Oxepa or immunex or cubitan or dipeptiven or omegaven or Reconvan or anom or oligopeptic or prosure* or Prem-8 or racol or RAC or rakol or ((impact or crucial) and (nestle or novartis))).tw
35 32 or 33 or 34
36 20 and 35

(*Continued*)

nutri* or formul* or tpn or enteric or Nutraceutical* or tube* or pn or SEN or "Ensure Liquid*"):TI,AB,KY #33 MESH DESCRIPTOR Nutrition Therapy EXPLODE ALL TREES #34 MESH DESCRIPTOR Nutritional Support EXPLODE ALL TREES #35 MESH DESCRIPTOR Dietary Supplements EXPLODE ALL TREES #36 MESH DESCRIPTOR Food, Formulated EXPLODE ALL TREES #37 #32 OR #33 OR #34 OR #35 OR #36 #38 #31 AND #37 #39 (immunonutri* or immunoenhanc* or imn or ied or Pharmaconutri* or immune-modulat* or immunomodulat* or IMEN or immunoenteral or IEEN or ien or immunodiet* or ((immune* or immuno*) near (enhanc* or enrich*)) or immunoenrich* or ief or ieef):TI,AB,KY #40 (isosource or jevity or vivonex or osmolite or nutrison or rna or Ribonucleic or "oral impact" or replete or alitraQ or immun-aid or optimental or perative or pivot or stresson or immunaid or nutrisource or Oxepa or immunex or cubitan or dipeptiven or omegaven or Reconvan or anom or oligopeptic or prosure* or Prem-8 or racol or RAC or rakol or ((impact or crucial) and (nestle or novartis))) #41 #38 OR #39 OR #40 #42 #22 AND #41	#37 (#30 AND #36) #38 (immunonutri* or immunoenhanc* or imn or ied or Pharmaconutri* or immune-modulat* or immunomodulat* or IMEN or immunoenteral or IEEN or ien or immunodiet* or immunoenrich* or ief or ieef[Title/Abstract]) #39 (immune* enhanc* or immune* enrich* or immuno* enhanc* or immuno* enrich*[Title/Abstract]) #40 (isosource or jevity or vivonex or osmolite or nutrison or "oral impact" or replete or alitraQ or immun-aid or optimental or perative or pivot or stresson or immunaid or nutrisource or Oxepa or immunex or cubitan or dipeptiven or omegaven or Reconvan or anom or oligopeptic or prosure* or Prem-8 or racol or RAC or rakol[Title/Abstract]) #41 ((impact or crucial[Title/Abstract])) AND (nestle or novartis[Title/Abstract]) #42 (#37 OR #38 OR #39 OR #40 OR #41) #43 (#22 AND #42)	

Web of Science (Web of Knowledge)	**CINAHL (EBSCO)**	**Trial Registries**
#1 **TOPIC:** (larynx or laryngeal or glottis or glottic or "oral cavity" or nasopharynx or nasopharyngeal or hypopharynx or hypopharyngeal or pharynx or pharyngeal or parapharyngeal or mouth or face or facial or oesophageal or esophageal or oesophagus or esophagus or thyroid or salivary or paranasal or "aero digestive" or aerodigestive or aero-digestive or (head near/3 neck)) #2 **TOPIC:** (cancer* or carcinoma* or neoplasm* or tumor* or tumour* or metastas*) #3 **TOPIC:**	S40 S22 AND S39 S39 S36 OR S37 OR S38 S38 TX isosource or jevity or vivonex or osmolite or nutrison or "oral impact" or replete or alitraQ or immun-aid or optimental or perative or pivot or stresson or immunaid or nutrisource or Oxepa or immunex or cubitan or dipeptiven or omegaven or Reconvan or anom or oligopeptic or prosure* or Prem-8 or racol or RAC or rakol or ((impact or crucial) and (nestle or novartis)) S37 TX immunonutri* or immunoen-	**ICTRP** immunonutri* AND head AND neck or immunoenhanc* AND head AND neck or Pharmaconutri* AND head AND neck or immune-modulat* AND head AND neck or immunomodulat* AND head AND neck or immunoenteral AND head AND neck or immunodiet* AND head AND neck or immunoenrich*AND head AND neck or immune* AND enhanc* AND head AND neck OR immune AND enrich* AND head AND neck OR immuno* AND enhance* AND head AND neck OR

(*Continued*)

(surg* or resect* or reconstruct* or pharyngectomy or laryngopharyngectomy or laryngectomy or mandibulectomy or commando or esophagectomy or oesophagectomy or (neck and dissect*) OR ((free or myocutaneous) and flap))
#4 #3 AND #2 AND #1
#5 **TOPIC:** (Argininosuccinic* or Benzoylarginine* or Homoarginine* or Nitroarginine* or Tosylarginine* or Methylarginine* or NO2Arg or NOARG or L-NMMA or D-NMMA or TAME or Proglumide* or Xylamide* or Xilamide or Milid or PUFA* or "n-3 fatty acid*" or Docosahexaen* or Neuroprostane* or Icosapentaenoic* or Timnodonic or Linoleic* or Linolenic* or Octadecadienoic* or Linoleate* or Linoelaidic or "n-6 fatty acid*" or Eicosapentaenoic or EPA or O-3FA* or O-6FA*)
#6 (enteral or polymeric* or Parenteral or diet* or feed* or food* or supplement* or nutri* or formul* or tpn or enteric or Nutraceutical* or tube* or pn or SEN or "Ensure Liquid*")
#7 #6 AND #5
#8 **TOPIC:** (immunonutri* or immunoenhanc* or imn or ied or Pharmaconutri* or immune-modulat* or immunomodulat* or IMEN or immunoenteral or IEEN or ien or immunodiet* or ((immune* or immuno*) near/6 (enhanc* or enrich*)) or immunoenrich* or ief or ieef)
#9 **TOPIC:** (isosource or jevity or vivonex or osmolite or nutrison or "oral impact" or replete or alitraQ or immun-aid or optimental or perative or pivot or stresson or immunaid or nutrisource or Oxepa or immunex or cubitan or dipeptiven or omegaven or Reconvan or anom or oligopeptic or prosure* or Prem-8 or racol or RAC or rakol or ((impact or crucial) and (nestle or novartis)))
#10 #9 OR #8 OR #7
#11 #10 AND #4

hanc* or imn or ied or Pharmaconutri* or immune-modulat* or immunomodulat* or IMEN or immunoenteral or IEEN or ien or immunodiet* or ((immune* or immuno*) N6 (enhanc* or enrich*)) or immunoenrich* or ief or ieef
S36 S30 AND S35
S35 S31 OR S32 OR S33 OR S34
S34 (MH "Food, Formulated+")
S33 (MH "Dietary Supplements+")
S32 (MH "Nutritional Support+")
S31 TX enteral or polymeric* or Parenteral or diet* or feed* or food* or supplement* or nutri* or formul* or tpn or enteric or Nutraceutical* or tube* or pn or SEN or "Ensure Liquid*"
S30 S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
S29 TX Argininosuccinic* or Benzoylarginine* or Homoarginine* or Nitroarginine* or Tosylarginine* or Methylarginine* or NO2Arg or NOARG or L-NMMA or D-NMMA or TAME or Proglumide* or Xylamide* or Xilamide or Milid or PUFA* or "n-3 fatty acid*" or Docosahexaen* or Neuroprostane* or Icosapentaenoic* or Timnodonic or Linoleic* or Linolenic* or Octadecadienoic* or Linoleate* or Linoelaidic or "n-6 fatty acid*" or Eicosapentaenoic or EPA or O-3FA* or O-6FA*
S28 (MH "Dietary Fiber")
S27 (MH "Nucleotides+")
S26 (MH "Glutamine")
S25 (MH "Fatty Acids, Omega-6+") OR (MH "Fatty Acids, Omega-3+")
S24 TX immuno or arginine* or glutamine* or nucleotide* or omega-3 or omega3 or omega-6 or omega6 or "*ω*-3" or nucleoside* or fibre* or fiber* or IMP1000 or IMP500 or immunostimulat* or immuno-stimulat*
S23 (MH "Arginine")
S22 S1 OR S2 OR S21
S21 S13 AND S20
S20 S14 OR S15 OR S16 OR S17 OR S18 OR S19
S19 (MH "Neck Dissection")
S18 TX (free or myocutaneous) and flap

immuno* AND enrich* AND head AND neck
ClinicalTrials.gov (via clinicaltrials.gov)
immunonutrition OR immunoenhanced OR Pharmaconutrition OR immunomodulated OR immunomodulating OR immunoenteral OR immunodiet OR immunoenriched OR ((immuno OR immune) AND (enhanced OR enriched OR enhancing OR enriching)) OR immune-modulating OR immune-modulated OR imn OR ied OR IMEN OR IEEN OR ien OR ief OR ieef
+
Condition: head and neck
ClinicalTrials.gov (Cochrane ENT Register)
1 (immuno or arginine* or glutamine* or nucleotide* or omega-3 or omega3 or omega-6 or omega6 or "*ω*-3" or nucleoside* or fibre* or fiber* or IMP1000 or IMP500 or immunostimulat* or immuno-stimulat*):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT
2 (Argininosuccinic* or Benzoylarginine* or Homoarginine* or Nitroarginine* or Tosylarginine* or Methylarginine* or NO2Arg or NOARG or L-NMMA or D-NMMA or TAME or Proglumide* or Xylamide* or Xilamide or Milid or PUFA* or "n-3 fatty acid*" or Docosahexaen* or Neuroprostane* or Icosapentaenoic* or Timnodonic or Linoleic* or Linolenic* or Octadecadienoic* or Linoleate* or Linoelaidic or "n-6 fatty acid*" or Eicosapentaenoic or EPA or O-3FA* or O-6FA*):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT
3 #1 OR #2 AND INSEGMENT
4 (enteral or polymeric* or Parenteral or diet* or feed* or food* or supplement* or nutri* or formul* or tpn or enteric or Nutraceutical* or tube* or pn or SEN or "Ensure Liquid*"):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT
5 #3 AND #4
6 (immunonutri* or immunoenhanc* or imn or ied or Pharmaconutri* or im-

(*Continued*)

	S17 TX neck and dissect* S16 TX pharyngectomy or laryngopharyngectomy or laryngectomy or mandibulectomy or commando or esophagectomy or oesophagectomy S15 TX surg* or resect* or reconstruct* S14 (MH "Surgery, Operative+") S13 S3 OR S4 OR S12 S12 S8 AND S11 S11 S9 OR S10 S10 (MH "Neoplasms+") S9 TX cancer* or carcinoma* or neoplasm* or tumor* or tumour* or metastas* S8 S5 OR S6 OR S7 S7 TX face or facial or oesophageal or esophageal or oesophagus or esophagus or thyroid or salivary or paranasal or "aero digestive" or aerodigestive or aero-digestive S6 TX larynx or laryngeal or glottis or glottic or "oral cavity" or nasopharynx or nasopharyngeal or hypopharynx or hypopharyngeal or pharynx or pharyngeal or parapharyngeal or mouth S5 TX head N3 neck S4 (MH "Otorhinolaryngologic Neoplasms+") S3 (MH "Head and Neck Neoplasms+") S2 (MH "Otorhinolaryngologic Neoplasms+/SU") S1 (MH "Head and Neck Neoplasms+/SU")	mune-modulat* or immunomodulat* or IMEN or immunoenteral or IEEN or ien or immunodiet* or immunoenrich* or ief or ieef):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT 7 ((immune* or immuno*) near (enhanc* or enrich*)):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT 8 (isosource or jevity or vivonex or osmolite or nutrison or rna or Ribonucleic or "oral impact" or replete or alitraQ or immun-aid or optimental or perative or pivot or stresson or immunaid or nutrisource or Oxepa or immunex or cubitan or dipeptiven or omegaven or Reconvan or anom or oligopeptic or prosure* or Prem-8 or racol or RAC or rakol):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT 9 ((impact or crucial) and (nestle or novartis)):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT 10 #5 OR #7 OR #6 OR #8 OR #9 11 (nct*):AU AND INSEGMENT 12 #10 AND #11

CONTRIBUTIONS OF AUTHORS

Noah Howes (NH), Charlotte Atkinson (CA), Steven Thomas (ST), Stephen J Lewis (SJL).

- Conceiving the review: NH, SJL and ST
- Designing the review: NH, SJL and ST
- Co-ordinating the review: NH and CA
- Undertaking manual searches: NH and SJL
- Screening search results: NH, CA, SJL and ST
- Organising retrieval of papers: SJL
- Screening retrieved papers against inclusion criteria: NH, CA, SJL and ST
- Appraising quality of papers: NH, CA, SJL and ST

- Abstracting data from papers: NH, CA, SJL and ST
- Writing to authors of papers for additional information: SJL
- Obtaining and screening data on unpublished studies: SJL
- Data management for the review: NH, CA and SJL
- Entering data into Review Manager (RevMan 5.3): NH and SJL
- RevMan statistical data: NH, CA, SJL and ST
- Other statistical analysis not using RevMan: NH and ST
- Double entry of data: (data entered by person one: NH; data entered by person two: ST)
- Interpretation of data: NH, CA, SJL and ST
- Writing the review: NH, CA, SJL and ST
- Providing guidance on the review: JB, SJL and ST
- Securing funding for the review: N/A
- Performing previous work that was the foundation of the present study: SJL and ST
- Guarantor for the review (one author): SJL
- Person responsible for reading and checking review before submission: NH

DECLARATIONS OF INTEREST

Noah Howes: no known conflicts of interest to declare.

Charlotte Atkinson: no known conflicts of interest to declare.

Steven Thomas: Steven Thomas was involved in the design, conduct and publication of a study of postoperative feeding in colorectal surgery (Lidder 2013) - funding support for that study was provided by Nutricia Ltd. He has no pecuniary interest in the product used in any of the studies.

Stephen J Lewis: Stephen J Lewis was involved in the design, conduct and publication of a study of postoperative feeding in colorectal surgery (Lidder 2013) - funding support for that study was provided by Nutricia Ltd. He has no pecuniary interest in the product used in any of the studies.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have made the following changes from the protocol (Howes 2014):

- Authorship has changed from: Noah Howes, Stephen J Lewis, Steven Thomas to Noah Howes, Charlotte Atkinson, Steven Thomas, Stephen J Lewis.
- The Background has been reworked and updated.
- The outcome wound infection/fistula has been separated into two separate outcomes.
- We have clarified the measurement of some of the outcomes as follows:
  - wound infections "as measured by the proportion of patients in whom any type or degree of wound infection was recorded, at any point postoperatively";
  - fistula formation "as measured by the proportion of patients in whom a fistula was recorded at any point postoperatively";
  - adverse events/tolerance of feeds "as defined by trial authors: as measured by the proportion of patients in whom adverse events relating to tolerance of feed was recorded, at any point postoperatively";
  - all-cause mortality "as measured by the proportion of patients recorded as having died at any point postoperatively";
  - postoperative complications as defined by trial authors "as measured by the proportion of patients in whom any type or degree of complication (other than wound infection, fistula formation or relating to tolerance of feed) was recorded, at any point postoperatively".
- We added "tolerance of feeds, as defined by trial authors" to the outcome "Adverse events" so that it now reads "Adverse events/ tolerance of feeds, as defined by trial authors".
- We added the following clarifying statement to Types of outcome measures: "We assessed the following outcomes in the review, but we did not use them as a sole basis for excluding studies".
- We have added a description of the method used to create a 'Summary of findings' table and carry out GRADE quality assessment.
- We did not conduct the planned sensitivity analysis to look at trial influence by sequentially excluding each trial due to the increased potential for obtaining spurious low P values resulting from repeated analyses.
- We did not conduct the planned subgroup analysis of "preoperative immunonutrition versus placebo drink" because only one study (with three treatment groups) gave pre-operative immunonutrition alone in one group (Falewee 2014). However, eight studies gave immunonutrition pre- and postoperatively and the remaining 10 studies gave immunonutrition only postoperatively; we conducted analyses for these subgroups.
- We removed "Biochemical changes, as defined by trial authors" and "Immunological changes, as defined by trial authors" from the secondary outcomes and have not formally assessed these because very few papers commented on immunological and biochemical parameter changes, and in each paper the markers chosen were different and assessed at differing time intervals. Meta-analysis of the few papers was thus not possible. Given the expected profound influence of the operative inflammatory response on levels of such markers, their interpretation is not straightforward.