Nutritional prehabilitation in head and neck cancer: A systematic review

Linda A Cantwell (cantwell505@gmail.com)
University of Liverpool School of Health Sciences https://orcid.org/0000-0002-2585-5529
Emer Fahy
Clatterbridge Centre for Oncology NHS Foundation Trust: Clatterbridge Cancer Centre NHS Foundation Trust
Emily R Walters
University of Southampton
Joanne M Patterson
University of Liverpool School of Health Sciences

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Abstract

Purpose: Prehabilitation affords an opportunity to support the management of malnutrition that is strongly associated with head and neck cancer. The purpose of this systematic review was to identify the components of nutritional prehabilitation interventions and their effects on nutritional and health outcomes in head and neck cancer patients.

Methods: A comprehensive search was completed within Medline (including PubMed), CINHAL, Cochrane database, EMBASE, PRoQUEST, clinical trials registries and grey literature to identify studies involving a nutritional intervention pre-treatment in head and neck cancer patients receiving any form of curative therapy. Nutritional intervention was defined as a specified period pre-treatment and outcomes measures had to include assessment of nutritional status or body composition. Quality of included studies was assessed using Cochrane risk of bias 2.

Results: From 557 identified studies, two met the inclusion criteria. Due to the low number of studies a meta-analysis was not indicated. Both studies conducted a nutritional intervention using an "enriched formula" in malnourished patients prior to surgery. Neither study reported the intervention was effective for reducing weight loss, physical function, surgical complications, or length of stay versus the comparison.

Conclusion: There is limited nutritional prehabilitation research within head and neck cancer. An "enriched formula" provided in the prehabilitation period appears no more advantageous than routine standard nutritional formula in mitigating against the weight loss experienced in malnourished head and neck patient. Due to the malnutrition risks on diagnosis and the negative impact of poor nutritional status on clinical and functional outcomes robust nutritional prehabilitation research is required to inform clinical practice.

Introduction

Head and neck cancer (HNC) is a devastating diagnosis affecting many daily functions including eating and drinking, leading to substantial weight loss that can negatively impact treatment tolerance and mortality. Globally, HNC is the 6th commonest cancer including cancers of the pharynx, larynx, salivary glands, oral cavity and nasopharynx. In 2020, HNC accounted for over 900,000 new cases with the incidence in 2040 predicted to rise by 46.8% [1]. In 2018, over 60% of patients in England with oropharyngeal had advanced disease at diagnosis; significantly greater than the 20% average for all cancer cases [2]. Advanced HNC is strongly associated with low socioeconomic status, poor health status, malnutrition and consequently results in aggressive multi-modality treatments and reduced survival [3–5]. Deaths from HNC in England are sadly over 200% greater in those living in the most deprived compared to the least deprived areas [6].

Malnutrition is an independent risk factor for increased mortality from HNC and poor quality of life (QOL) outcomes [7–9]. Up to 60% of HNC patients are malnourished or at high risk of malnutrition at presentation [10]. Causes of malnutrition in HNC are multifactorial, ranging from the disease itself affecting the ability to eat and drink to negative health related behaviours such as high alcohol consumption [11, 12]. HNC treatments include surgery, radiotherapy (RT) and/or chemoradiotherapy (C)RT and can result in substantial side-effects such as dysphagia, odynophagia, oral mucositis, xerostomia, trismus, taste changes or nausea [13]. These side effects can be permanent and are associated with substantial weight loss [14, 15]. Therefore, interventions that can mitigate against significant weight loss are key to avoiding malnutrition as well as promoting and enhancing QOL and survivorship.

Prehabilitation enables patients to prepare for treatment by promoting healthy behaviours, maximising resilience to treatment and improving long-term health [16]. Prehabilitation is typically considered the time from diagnosis to commencement of cancer treatment.

Nutritional prehabilitation can take different forms including nutritional counselling (optimising intake of macro and micronutrients nutrients from dietary sources), oral nutritional supplements (ONS) (including high energy ONS, protein only supplements and immunonutrition) and enteral feeding (feed delivered through a feeding tube). It may be combined with other elements such as physical activity, behaviour change and/or psychological support, often referred to as multimodal prehabilitation [16, 17]. These interventions are complex, influenced by both context (i.e., social, economic, geographical, and cultural pressures) and systems (i.e. the care pathway) [18]. Several systematic reviews have explored elements of multimodal prehabilitation across different and mixed cancer sites [19–21] and older adults [22]. Evidence suggests that nutrition prehabilitation is a key factor in improving the functional status, QOL, and reducing post-operative complications in lung and colorectal cancer patients [23–25]. Introducing prehabilitation into the HNC pathway is challenging due to the burden of lengthy multimodal treatments that can often be delivered across different geographical sites in a population with complex clinical and psychosocial factors [3, 26]. While nutritional interventions delivered during HNC have been successful in mitigating against weight loss and improving QOL [27–29] nutritional prehabilitation remains a relatively new area of research.

The aim of this systematic review is to examine the evidence for a nutritional prehabilitation intervention alone or as part of a multimodal intervention on reported nutritional and health outcomes following treatment for HNC. The main research questions are:

1) What are the effects on nutritional status, body composition, physical function and patient reported outcome measures?

2) What are the components of the nutritional and other prehabilitation interventions?

3) Are single nutritional or nutrition as part of multimodal interventions more effective?

3) What is the compliance with the nutritional intervention?

Methods

This review was conducted in accordance with preferred reporting items for systematic reviews (PRISMA) guidance. The review protocol was registered with the international prospective register of systematic reviews (PROSPERO), Registration no. CRD42021248598.

Databases:

Searches were conducted online between 7th to 10th May 2021 within Medline (including PubMed), CINHAL, Cochrane database, EMBASE, and PRoQUEST. Clinical trials registries clinical trial.gov, WHO clinical trial, trialcentral.org and ISRCTN registry were also searched. Grey literature was searched using open grey, conference proceeding citation index, and relevant conference abstracts (BAHNO, NCRI and ESPEN). Reference list of included studies were hand searched. There was no search date restriction however publications had to be published or available in English.

The search strategy was as outlined below, and a sample full database search is available in the Appendix.

- Head and neck cancer **OR** Oropharyngeal **OR** HNC **OR** Throat cancer **OR** Oral Cancer

AND

- Prehab **OR** Prehabilitation **OR** Multi-modal prehabilitation **OR** Pre-treatment **OR** Preoperative **AND**
- Nutrition **OR** Dietary **OR** Nutritional Counselling **OR** Dietary Counselling **OR** Diet Therapy

Eligibility Criteria:

The study inclusion and exclusion criteria were defined using PICOs (Population, intervention, comparison, outcome, study type) and are outlined in Table 1.

Table 1
The PICO characteristics for inclusion and exclusion of studies

	Inclusion	Exclusion
Population	● Adults > 18years ● Diagnosis of head and neck cancer ● Receiving any combination of surgery, radiotherapy and /or chemoradiotherapy with curative intent	● Palliative care
Intervention	● Nutritional intervention ● Nutritional intervention must be clearly defined i.e., supplementation, energy or protein targets, or modifications ● Can be part of a single or multimodal intervention ● Undertaken for a defined or reported period before starting planned surgical or oncology treatment	● Exercise only ● Behaviour only ● Interventions that contain nutrition advice as part of a broader lifestyle intervention (i.e., relaxation, mindfulness) ● Use of parenteral nutrition ● Interventions started during treatment
Comparator	● Standard or usual care, a different active intervention, or no treatment	
Outcome	Validated measures of: ● Nutritional status ● Body composition ● Functional status ● Dietary intake ● Treatment complications ● QOL	● Do not contain any nutritional status/body composition outcomes
Study design	● All randomised control trials ● Observational or cohort studies to increase inclusion for synthesis	● Qualitative studies or single case reviews ● Abstract only

Study selection/screening:

All papers identified from the search strategy were transported to a reference manager software (EndNote™) and screened by the primary reviewer (LC) for duplicates. To enable blinding all remaining abstracts were then screened by two reviewers (LC/EF) using Rayyan (Rayyan systems inc.) and any discrepancies or uncertainties regarding eligibility were discussed with a third reviewer (EW). Full texts were then retrieved and read by the primary and secondary reviewer and eligibility was agreed with no discrepancies requiring the third reviewer.

Data extraction

Data was extracted independently by the primary reviewer (LC) and cross checked by the second reviewer (EF). Baseline study characteristics included the location of the study, study design, type of intervention (nutrition only or multimodal), clinical description and sample size. The template for intervention description and replication (TIDieR) checklist [30] was used to describe the study intervention.

The primary outcome was change in body composition as measured by change in weight, BMI or muscle mass. Secondary outcomes extracted if available were, change in nutrition risk or assessment score, objective measures of physical function using validated measures such as handgrip strength, six-minute walk test (6MWT) or time stand up and go, dietary intake, and any impact of the intervention on length of stay, treatment complication, survival and patient reported outcomes using a validated questionnaire. Authors of included studies were contacted to obtain data that wasn't available within the published manuscript.

Quality assessment:

The quality of each study was assessed independently by two reviewers (LC and EF) using the Cochrane Risk of Bias Tool 2 for randomised trials [31] using weight change as the specific outcome measure. Signalling questions were used alongside an algorithm to guide judgement of low risk of bias, some concern or high risk of bias within each of the five domains. Disagreements in risk of bias were discussed with the third reviewer (EW).

Data synthesis

Data was synthesised using narrative synthesis to textually describe and interpret the study findings. The synthesis without meta-analysis (SwiM) reporting guidance [32] was used throughout the process, to systematically answer the four research questions.

1) What are the effects on nutritional status, body composition, physical function and patient reported outcome measures?

2) What are the components of the nutritional and other prehabilitation interventions?

3) Are single nutritional or nutrition as part of multimodal interventions more effective?

4) What is the compliance with the nutritional intervention?

Results

Study selection

The primary literature search identified 530 articles from the database search of which, 209 duplicates were removed. A search of clinical trials registries identified 27 potential records however these did not meet the inclusion criteria. No articles were identified through hand searching. Following screening of titles and abstracts, six manuscripts were retrieved for full review. Following review of the full manuscript four studies were excluded. Two studies were excluded as they did not include the primary outcome measure [33, 34], one study included parenteral nutrition [35] and another study commenced the intervention at various points along the treatment journey and not solely during pre-treatment [36] Therefore, two papers [37, 38] met the full criteria for systematic review (Figure 1).

Study characteristics

Study characteristics are presented in Table 2. The studies had several comparable characteristics, both were randomised controlled trials that were conducted in malnourished surgical head and neck cancer patients as measured by weight loss of > 10% over the past 6 months [38] or with a score of ≥ 2 on the Malnutrition Screening Tool (MST) [37] and were nutrition only, single modal interventions. The main contrast was their year of publication which differed by 18 years and location of study. The total sample size was n=111.

Patient characteristics

Baseline patient characteristics are presented in Table 3. Studies included patients of similar ages; the majority were also male. The primary HNC sites in both studies were similar. Participants in one study [38] had advanced HNC (≥ tumour stage 3) and included recurrent tumours. In contrast, Jantharapattana & Orapipatpong,[37] included tumour stage 1-2 and no recurrent tumours, but the majority of patients recruited in this and by Van Bokhorst-De Van Der Schueren *et al.* [38] had tumour stage 4. Surgical treatment was either combined mandibular resection or total laryngectomy [38] or tumour resection with or without neck dissection and/or flap reconstruction [37]. Baseline, pre-intervention body weight and body composition was also similar across both studies.

The TIDieR checklist was used to summarise the intervention of each of the studies (Table 4). Both studies used an "enriched" nutritional supplement as part of their intervention. Jantharapattana & Orapipatpong, [37] used an eicosapentaenoic acid (EPA) enriched oral nutritional supplement, whereas Van Bokhorst-De Van Der Schueren *et al.*[38] used an arginine enriched enteral feeding formula delivered via a nasogastric tube. Both used a standard isocaloric formula as their comparison. Van Bokhorst-De Van Der Schueren *et al.* [38]had a third arm, group 1, which received no pre-operative nutrition support. Both studies collected anthropometric data and their primary outcome was nutritional status and weight change/body composition, at the end of the 7-day preoperative period [38] and during perioperative period, 7 days before surgery to 4 months after, [37]. Both studies estimated nutritional requirements using the Harris Benedict equation and instructed participants to keep a diet diary to monitor that estimated energy requirements (EER) were met throughout the study. Post operatively both studies continued to provide either the EPA supplement [37] or arginine enriched formula [38].

Good adherence to the protocol was demonstrated by 100% volume of oral nutritional supplements reportedly being consumed [37] and greater than 100% estimated requirements being met through enteral feeding over planned 7-10days [38] (Table 4) with a low attrition rate reported across both studies.

Table 2

The study characteristics of included studies

Author	Location	Study Design	Type of intervention	Clinical	Sample size (n)	Cancer Treatment
Jantharapattana & Orapipatpong, 2019[37]	Thailand	RCT	Nutrition only	Histologically proven diagnosis of HNC Score of ≥2 MST	62	Primary tumour resection or neck dissection or Primary tumour resection & flap reconstruction or Primary tumour resection & neck dissection & flap reconstruction
Van Bokhorst-De Van Der Schueren *et al.,* 2001 [38]	Amsterdam	RCT	Nutrition only	SCC of the oral cavity, larynx, oropharynx, or hypopharynx Malnourished weight loss> 10%	49	Combined mandibular resection or Total laryngectomy

MST, malnutrition screening tool; SCC, squamous cell carcinoma.

Table 3

Baseline patient characteristics of included studies

Author	Age mean, (SD)	Male, n (%)	Cancer stage, n (%)	Primary site, n (%)	Body weight, kg, mean (±SD)	BMI, kg/m^2 mean (±SD)	Handgrip strength, kg, mean (±SD)	Energy intake, kcal, mean	Lean body mass, mean (±SD)	Fat mass, mean (±SD)
Jantharapattana & Orapipatpong, 2019	**I:** 55.2 (13.5) **C:** 59.5 (13.4)	**I**: 24 (77.4) **C:** 26 (83.9)	**I:** T1, 2 (6.5); T2, 10 (32.3); T3, 4 (12.9); T4a, 14 (45.2); T4b, 1 (3.2). **C:** T1,5 (16.1); T2, 5 (16.1); T3, 5 (16.1); T4a, 15 (48.4); T4b, 1 (3.2)	**I:** Oral, 20 (64.5); Larynx, 5 (16.1); Oropharynx, 6 (19.4%). **C:** Oral, 16 (51.6); Larynx, 8 (25.8); Oropharynx, 4 (12.9); Hypopharynx, 2 (6.5); Unknown, 1 (3.2)	**I:** 58kg * **C:** 59kg	I: 22.3 (2.8) C: 21.2 (3.6)	Not measured	**I:** 1750** **C:** 1800	**I**: 45.1% (6.6) **C:** 41.1% (9)	**I:** 25.6% (7.6) **C:** 25.6% (8.9)
Van Bokhorst-De Van Der Schueren *et al*., 2001	**G1:** 55 (10) **G2:** 60 (8) **G3:** 59 (12)	**G1:** 11 (64.7) **G2:** 7 (46.7) **G3:** 12 (70.6)	**G1**: T3, 2 (11.8); T4a,11 (64.7); T4b, 1 (5.9); Recurrent, 3 (17.6) **G2**: T3, 2 (13.3); T4a, 7 (46.7); Recurrent, 5 (33.3); Not stage, 1 (6.7) **G3:** T3, 3 (17.6); T4a, 9 (52.9); Recurrent, 5 (29.4)	**G1:** Oral, 5 (29.4); Larynx, 3 (17.6); Oropharynx, 5 (29.4); Hypopharynx, 4 (23.5). **G2;** Oral, 2 (13.3); Larynx, 3 (20); Oropharynx, 4 (26.7); Hypopharynx ,5 (33.3); Other, 1 (6.7). **G3:** Oral, 1 (5.9); Larynx, 3 (17.6); Oropharynx, 9 (52.9); Hypopharynx, 3 (17.6); Other, 1 (5.9)	**G1**: 62.8 (8.4) **G2:** 55.3 (8.1) **G3:** 61.6 (8.5)	Not measured	**G1:** R, 35.3 (10.6); L, 27.9 (13.9) **G2:** R, 26.7 (9.5); L, 26.4 (11.0) **G3:** R, 33.6 (10.9); L 29.2 (14.6)	Not reported	**G1** 42.1kg (16.8) **G2:** 36.3kg (17.0) **G3:** 47.5kg (6.9)	**G1:** 12.2kg (8.7) **G2:** 10.5kg (6.7) **G3:** 13.0kg (5.8)

G1: Group one, no preoperative nutrition support; G2: Group 2, standard preoperative enteral nutrition; G3: Group 3, Arginine enriched enteral nutrition: I, intervention; EPA, enriched supplement; C, comparison, standard nutritional supplement; T1, Stage one; T2, Stage 2; T3, Stage three; T4, Stage four; BMI, Body mass index; R, right arm; L, Left arm.

* Estimated value extracted from figure 3 in Jantharapattana & Orapipatpong [37]

** Estimated value extracted from figure 2 in Jantharapattana & Orapipatpong [37]

Quality/ Risk of bias

Risk of bias is summarised in Figure 2. Cochrane ROB 2 analysis identified Van Bokhorst-De Van Der Schueren *et al.*[38] as high risk due to concerns raised in domain two, deviations from intended treatment and domain five, risk of bias in selection of the reported results. Van Bokhorst-De Van Der Schueren *et al.* [38]had planned to recruit n=39 per group however they failed to recruit to even 50% of this in each group citing slow recruitment and end of finances. No information was given as to why recruitment was slow leading to reviewers concerns regarding protocol development and the intended recruitment process. In addition, the authors reported collecting weight as an outcome at day 1, 4 and 7 post operatively and on discharge however this data are unpublished. Jantharapattana & Orapipatpong[37] was identified in all domains and overall, as low risk of bias.

Table 4

Intervention characteristics of the included studies according to TIDieR checklist

Study	Intervention name	Comparison	Why	What (material)
Jantharapattana & Orapipatpong, 2019	Efficacy of preoperative EPA-enriched ONS in HNC	Standard iso caloric ONS	Study the weight change effects of an EPA-enriched supplement compared with a conventional supplement in malnourished patients with HNC	EPA containing ONS, (Prosure, Abbott Laboratories Ltd., Zwolle, the Netherland)
Van Bokhorst-De Van Der Schueren *et al.,* 2001	Perioperative arginine enriched enteral feeding in HNC	**G1:** No pre-operative nutrition support **G2:** standard formula preoperative EN	Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function and postoperative morbidity, and survival in severely malnourished HNC patients	NG tube placed in intervention, (G3) and comparison (G2) groups An arginine enriched EN formula. A standard formula EN formula.

Intervention characteristics continued.

What (procedure)	Who provided	How (mode of delivery)	Where
Instructed to consume an EPA enriched (or standard isocaloric) ONS for 7-10 days preoperatively. Also continued for 14 days postoperatively. All patients requested to record nutritional intake in a diet diary	Not reported	Intervention was delivered individually. Face to face appointment to obtain baseline data, biochemistry and complete history taking. Post operatively clinical assessment was performed and recorded daily.	ONS consumed preoperatively at home. Post-operative supplements were consumed in hospital
Preoperatively, (G2 and G3) received full EER by EN. Were allowed to eat in addition as desired. G1, directed to continue their usual oral diet All patients requested to record nutritional intake in a diet diary	Recruitment through a research dietitian. Patients had at least one telephone contact with the research dietitian preoperatively	The intervention was delivered individually. Enteral nutrition through a NG tube. Preoperative telephone call with the research dietitian.	EN was taken at home unless clinically contraindicated and hospital admission required. Post-operative EN was taken in the hospital.

Intervention characteristics continued.

When and how much	Tailoring	Modification	How well (planned)	How well (actual)
EPA enriched ONS, 2.2g EPA and 630kcal consumed for 7-10days preoperatively and 14 days post operatively	EER calculated based on the Harris-Benedict equation	None reported	The volume of ONS consumed was recorded in diet diary. Calculated sample size based on 2-tailed test with a significance 0.05 and 0.8 power was n=31 per group.	65 patients finished the trial and consumed allocated supplements. Three patients lost to follow up.
For 7-10days pre surgery to meet EER G3: enriched EN formula (41% of casein was replaced with arginine). G2: isocaloric and isonitrogenous standard formula All groups received EN from day one to ten postoperatively	EER calculated as: 1.5 x Harris-Benedict BMR equation using actual weight	None reported	Nutritional intake was recorded in a diary. Calculated sample size n= 39 per study group with 80% power and 5% significance.	Preoperatively G2 and G3, achieved 110% and 113% of their EER, respectively. Preoperative tube feeding provided for 8.8 ± 1.4 days (G2) and 8.6 ± 1.4 days (G3) met the planned 7-10days. Energy intake was mostly from tube feeding as planned. Due to slow patient recruitment and financial reasons the study ended with low sample size n=49

G1: Group one, no preoperative nutrition support; G2: Group two, standard preoperative enteral nutrition; G3, Group three, Arginine enriched enteral nutrition; EN, Enteral nutrition; EER, estimated energy requirements; EPA, Eicosapentaenoic acid; QOL, quality of life; NG, Nasogastric; ONS, oral nutritional supplement.

The effects on nutritional status, body composition, physical function, and patient reported outcome measures?

The primary outcome of interest in both studies was change in body weight. Both studies demonstrated no significant differences in change in body weight between intervention and comparison/control groups, following the 7-10day period of preoperative intervention (Table 5). At four-month follow-up Jantharapattana & Orapipatpong[37] demonstrated no difference in body weight between groups. Post-surgical or long-term changes in body weight were unreported by Van Bokhorst-De Van Der Schueren *et al.*[38]. However, in post hoc analysis of survival, greater preoperative significant weight loss (16.5%) predicted mortality, versus 12.4% weight loss in those who survived (p=0.034).

Equally no changes were observed in fat and lean body mass measured by BIA, in the preoperative and follow up periods. Van Bokhorst-De Van Der Schueren *et al.*[38] reported no change between the two groups in physical function using handgrip strength measured with a Jamar Dynamometer.

Nutritional status as measured by a validated assessment tool such as PG-SGA [39] was not used in either study.

There were also no significant differences in post operative complications and LOS between groups in both studies (Table 5). Neither study collected any QOL patient reported outcome measures for synthesis or discussion.

Table 5

The intervention results of the included studies

Study	Change in body weight, kg, mean (±SD)	Change in fat free mass, mean	Change in handgrip strength, kg, mean (±SD)	Energy Intake	Surgical complications, n, (%)	Length of stay	Survival
Jantharapattana & Orapipatpong, 2019 [37]	Preoperatively, day 1-7 **I:** no change* **C:** 0.4 * At 4 months post treatment **I:** -2.95 (4.7) **C**: - 2.82 (4.78) Overall weight change 2.89, 5%	Preoperatively, day 1-7: No change within or between groups At 4 months post treatment **I:** -2.16 % (±SD 3.78) **C:** - 1.25 (±SD 4.43) Overall change - 1.73%	Not measured	**Change in mean calorie intake Preoperatively, day 1-7 **I:** 50kcal **C:** 100kcal At 21days **I:** 550kcal **C:** 550kcal	Pulmonary infections **I:** 2 (6.5) **C**: 0 Urinary infections **I**: 0 **C**: 0 Surgical infections **I**: 4 (12) **C**: 5 (16.1) Wound complications **I:** 4 (12.9) **C:** 7 (22.6)	**I:** median 7 (IQR 6-12) **C:** median 8 (IQR 6-12.5)	Not measured
Van Bokhorst-De Van Der Schueren *et al.,* 2001[38]	Baseline to 1 day preoperatively **G1**: -0.1 **G2**: 0.5 **G3**: 0.7	Baseline to 1 day preoperatively **G1**: - 0.3kg **G2**: 2.5kg **G3:** 0.7kg	Baseline to 1 day preoperatively Right Arm **G1**: -0.9 **G2:** -0.1 **G3:** 0.5 Left Arm **G1:** 1.6 **G2:** -1.3 **G3**: 1.3	Baseline to 1 day preoperatively **G2**: 110% EER **G3:** 113% EER **G1:** 79% EER (p = 0.007) -	Major surgical complications **G1**: 9 (53) **G2:** 7 (47) **G3:** 10 (59)	**G1**: mean 41 (±SD 32) G**2**: mean 46 (±SD 30) **G3:** mean 31 (±SD 23)	Overall Survival 35% **G3**: better survival trend (p= 0.15) % Weight loss Survivors: 12.4% Died: 16.5 % (p= 0.034)

I, intervention, EPA enriched supplement; C, comparison, isocaloric nutritional supplement; G1: Group 1, no preoperative nutrition support; G2: Group 2, standard preoperative enteral nutrition; G3: Group 3, Arginine enriched enteral nutrition; EER, Estimated Energy Expenditure

*Estimated value extracted from figure 3 in Jantharapattana & Orapipatpong [37]

** Estimated value extracted from figure 2 in Jantharapattana & Orapipatpong [37]

The components of the nutritional and other prehabilitation interventions

Both studies investigated the use of an “enriched” nutritional formula. Jantharapattana & Orapipatpong[37] used an ONS which contained 2.2g of EPA. EPA is a n-3 polyunsaturated fatty acid purported to reduce pro-inflammatory cytokines and modulate changes in nutritional status [40, 41]. The EPA enriched ONS was given to the intervention participants to drink orally in addition to continuing their normal dietary intake before surgery. In contrast Van Bokhorst-De Van Der Schueren *et al.*[38] used the nutritional intervention to meet the participants full EER via a nasogastric feeding tube. Van Bokhorst-De Van Der Schueren *et al.*[38] used an enteral formula which had a greater composition level of the amino acid arginine, replacing 41% of the casein. Arginine is proposed to have a positive impact on the immune response and therefore improve surgical outcomes [42, 43]. Both studies conducted the pre-treatment intervention over a similar period, 7-10days. Preoperative tube feeding was provided for 8.8 ± 1.4 d (group 2) and 8.6 ± 1.4 d (group 3) [38], whilst the oral nutritional supplements were reported to have been consumed for at least seven days [37]. Both studies also provided nutrition support interventions for comparable lengths of time during the postoperative period, 14 days [37] and 10 days [38] until assurance of no anastomotic leaks was provided using oral video fluoroscopic swallow x-rays. It is assumed they therefore returned to oral intake however there was no details given regarding the process for example, was there a gradual reduction in enteral feeding to allow transition to oral diet? The intervention by Van Bokhorst-De Van Der Schueren *et al.*[38] also included a telephone appointment with the dietitian, however the details of the purpose of the call or advice provided was not clearly described. Neither study contained any other elements of prehabilitation such as exercise or psychological input.

Are single or multimodal interventions including nutrition more effective at improving health outcomes?

The systematic review did not identify any multimodal interventions which included a nutritional intervention therefore this research question cannot be answered.

Compliance with the intervention

Good compliance with the nutritional intervention was reported across both studies according to patient records of daily intake using a diet log. Jantharapattana & Orapipatpong[37] reported that all patients consumed their prescribed ONS throughout the preoperative and perioperative period. In addition, estimated energy requirements were reported to be met throughout the study and caloric intake did not differ significantly between the intervention (1750kcal at baseline; 2300kcal at 21days) and control groups (1800kcal at baseline; 2350kcal at 21days).

Participants in the study by Van Bokhorst-De Van Der Schueren *et al.*[38] maintained enteral feeding for 8.8 ± 1.4 days (group 2) and 8.6 ± 1.4 days (group 3) preoperatively, which was within the planned 7-10 days. Preoperatively enteral feeding was at home, unless clinically indicated, however the authors did not provide any quantitative data for this. The intervention group 3 met 113% of their EER while the comparison (group 2) and control (group 1) met 110% and 79% (P=0.007) respectively.

Discussion

This systematic review identified two RCTs testing nutrition prehabilitation in pre-surgical HNC patients who were malnourished. Both interventions introduced enriched oral or enteral nutritional supplements preoperatively, and neither showed demonstrable differences in weight or body composition. Furthermore, there were no significant differences in surgical complications or LOS. No identified studies included physical activity or any other prehabilitation component alongside a nutritional intervention. Additionally, there were no nutritional prehabilitation studies conducted in patients undergoing primary oncology HNC treatment.

Nutritional status

Neither study demonstrated that enriched oral or enteral feeding were effective at improving nutritional status or functional outcomes when provided for 7-10days preoperatively. Jantharapattana & Orapipatpong[37] presented four-month follow up data on weight loss. Weight loss in both intervention and control groups was minimised to five percent, but with no demonstrable difference between the two groups. However, groups were not stratified for adjunctive (C)RT treatment, which could substantially impact on longer term nutritional parameters. Both studies reported low levels of surgical complications and LOS irrespective of the type of nutritional support provided (enriched or standard isocaloric equivalent) and also if no preoperative nutrition support was provided[38]. Although energy intake of the control group (group 3) was statistically lower than others ($p < 0.007$) they still reached nearly 80% of EER before treatment and were provided with post operative enteral feeding [38]. This suggests that optimal nutritional intake and nutritional interventions provided prior to and during hospitalisation may reduce the negative impacts of treatment. Meeting estimated nutritional requirements may be just as important as introducing “enriched” ONS or enteral feed.

The principles of prehabilitation acknowledge that all patients should be screened for malnutrition risk using a validated tool and offered support based on their individual needs [16]. Nutritional challenges are associated with complex surgery and/or (C)RT and therefore, the majority of HNC patients are at risk, indicating a need for early nutrition support interventions, enabling them to withstand acute and chronic treatment side effects [44]. Both studies in this review limited recruitment to those with pre-exiting malnutrition, which may have limited the effect of the interventions under investigation. Research has shown that nutritional interventions provided during (C)RT can reduce weight loss, treatment interruptions and improve overall survival even in non-malnourished HNC patients [36] .

Nutritional intervention

This systematic review found insufficient information to identify the essential components of a successful nutritional prehabilitation intervention for HNC patients. Many elements of the assessment and intervention were poorly described across both studies, making it difficult to replicate. Jantharapattana & Orapipatpong[37] failed to report who undertook the physical examinations, calculated EER, and delivered the nutritional intervention. Some detail was provided by Van Bokhorst-De Van Der Schueren *et al.*[38] i.e. the intervention was delivered by a research dietitian, who contacted patients by telephone at

least once, although the content of this consultation was not described. Evidence suggests that better nutritional status, function and QOL outcomes are achieved if nutritional interventions are personalised and delivered intensively by dietitians rather than nurses [44, 45].

No validated nutritional assessment tool was used in either study and both failed to reference any recommended nutritional care standards or guidelines. Consideration was given only to meeting patients' estimated energy requirements and no acknowledgement was given to protein or other micro or macronutrient requirements. European and international guidelines in oncology and HNC recommend estimating energy requirements based on at least 25-30kcal/kg/day and protein requirements at least 1.2-1.5g/kg/day of body weight [46–48]. Indeed, some studies suggest that energy and protein requirements for HNC patients undergoing treatment is greater than these due to the considerable weight loss[49] and loss of lean mass[50] identified. However, while it is agreed that protein requirements are increased in this patient group, sufficient data on the quality of protein[46] and timing of delivery are scarce and mixed.

Estimated energy requirements can vary according to the assessment method [51]. In this review, both studies[37, 38] used the Harris-Benedict predictive equation. Van Bokhorst-De Van Schueren *et al*.[38] added an activity factor of 1.5, however this was generalised across all patients irrespective of any estimates of physical activity. Neither study stated if a stress factor was applied or if additional considerations were given to increased energy and protein intake to support repletion. This is particularly relevant given that the patients were malnourished, and this is an important factor in any dietetic assessment and estimation of nutritional requirements.

Both studies have suggested that their pre-surgical nutritional intervention in this population may not have been sufficient to induce significant changes in nutrition status. There is a consensus amongst guidelines that nutrition support provided by a dietitian is initiated before (C)RT [46–48]. However, these do not provide recommendations on the length of time before treatment, intensity, and location of nutrition support delivery. Minimal information on the timing and location of the intervention delivery was provided in the two studies [37, 38]. Enteral nutrition was reported to be delivered at the patient's home unless medical circumstances required hospital admission. No information was given regarding what these circumstances were nor how many patients were admitted. In addition, there was no information on refeeding risk - a known metabolic disturbance in malnourished HNC patients [52, 53]. Others have commented on poor descriptors of nutritional care and inconsistency of reporting being a common issue in nutritional prehabilitation research [17, 54]. In response, Gillis *et al*.[54] have recommended a systematic Nutrition Care Process Model approach and development of a core set of outcomes to improve the quality of studies and facilitate pooling of future evidence.

In summary, although no evidence for introducing an enriched formula pre-treatment was reported, this could be due to several limitations in study design such as the extent of malnutrition at point of nutritional intervention, length of nutritional intervention, lack of prescribed anabolic stimulus such as exercise or that an increase in calories, protein or micronutrients rather than immune enhancing additives are more important.

Physical activity

This systematic review did not identify any studies where prehabilitation in HNC patients combined physical activity and nutritional interventions. These interventions can be seen as synergistically related. Malnutrition is associated with poor functional performance[55] therefore patients undertaking exercise only prehabilitation may have difficulties engaging with exercise to improve performance compared to those that are well nourished [56]. A short seven-day prehabilitation study in a mixed cohort of abdominal and HNC surgical patients[57] compared with matched controls receiving no prehabilitation investigated a programme including impact breathing techniques, consumption of an ONS three times daily (280kcal, 26g protein/ 250ml serving), and a daily target of 7,500 steps. Reported compliance with ONS was high however the study did not account for changes in dietary oral intake as a result of the intervention. In contrast compliance with exercise was low, only 22% reached the step target. Significant improvements in post-operative mobility and decreased incidence of pulmonary morbidity were demonstrated in prehabilitation versus no prehabilitation group. No differences ionin overall infections, LOS, or hospital readmission was found. No functional, QOL or nutritional status outcomes were reported and therefore this study was excluded from this review.

Two systematic reviews have investigated 1) the effects of nutritional and physical exercise interventions *during* radiotherapy[58] and 2) physical activity only in HNC patients receiving multi-modality treatment[59]. Bye *et al*.[58] concluded that a combined intervention improved body composition, physical function, and nutritional status [58]. However, the interventions were highly heterogeneous, making it difficult to provide recommendations for which physical or nutritional interventions to introduce. Several pilot or feasibility studies were identified, demonstrating that this type of intervention was acceptable, but were too small to provide sufficient evidence of effectiveness. Capozzi *et al*.[59] identified eight physical activity intervention studies. Improvements in patient reported outcomes of QOL and fatigue in addition to body composition and physical function was identified. None of the studies implemented physical activity interventions prior to treatment and timing of the interventions was highly heterogeneous occurring during or following treatment, both during and post treatment or unspecified. Despite this the findings suggest that physical activity in HNC patients is likely to be safe, feasible and beneficial during chemotherapy or radiotherapy treatment. Ultimately, there remains a need for better quality data from well-designed RCTs that combine physical activity and nutritional interventions during the prehabilitation period in HNC to identify if this multimodal combination is both feasible and more effective than a single approach.

Limitations:

Due to the small number of papers identified no meta-analysis could be completed. In addition, limitations within the studies themselves including being poorly powered and methodological uncertainties mean that it's difficult to make any recommendations regarding the most effective components for nutritional prehabilitation interventions in HNC. We attempted to contact the authors to obtain further raw data, although there was no response this wouldn't have impacted the results. A strength however is that all studies that met the inclusion criteria were included, none were excluded due to language or lack of access to a full manuscript.

Conclusion

HNC patients are at high risk of malnutrition on diagnosis which is likely to worsen during treatment. Preliminary data of nutritional and multimodal interventions in HNC introduced pre surgery, during radiotherapy/(C)RT or post-treatment show that they are achievable, safe and may have a positive impact on clinical, nutritional and functional outcomes. This systematic review found that providing “enriched” nutritional supplements or enteral nutrition pre-treatment did not improve nutritional outcomes in surgical HNC patients, however, there were substantial limitations in study design. An agreed set of core outcome measures is indicated to generate high quality evidence. Robust nutritional and multi-modality prehabilitation studies are needed to evaluate the effectiveness of this intervention, evaluating its essential components, optimal delivery mechanisms and pathway to implementation in this vulnerable patient group.

Declarations

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Competing Interests

All authors have no relevant financial or non-financial interests to disclose

Author Contributions

The initial conception was from Linda Cantwell. All authors then contributed to study design. Material preparation, data collection and analysis were performed by Linda Cantwell, Emer Fahy and Emily Walters. The first draft of the manuscript was written by Linda Cantwell and all authors commented on previous versions. All authors read and approved the final manuscript.

Ethical Approval

This is a systematic review. No ethical approval required.

Availability of data and material

All data generated or analysed during this study are included in this published article or within supplementary files.

Coda availability

Not applicable as no software of coding was used

Consent to participate.

Not applicable as there were no human subjects

Consent for publication

Not applicable

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Figures

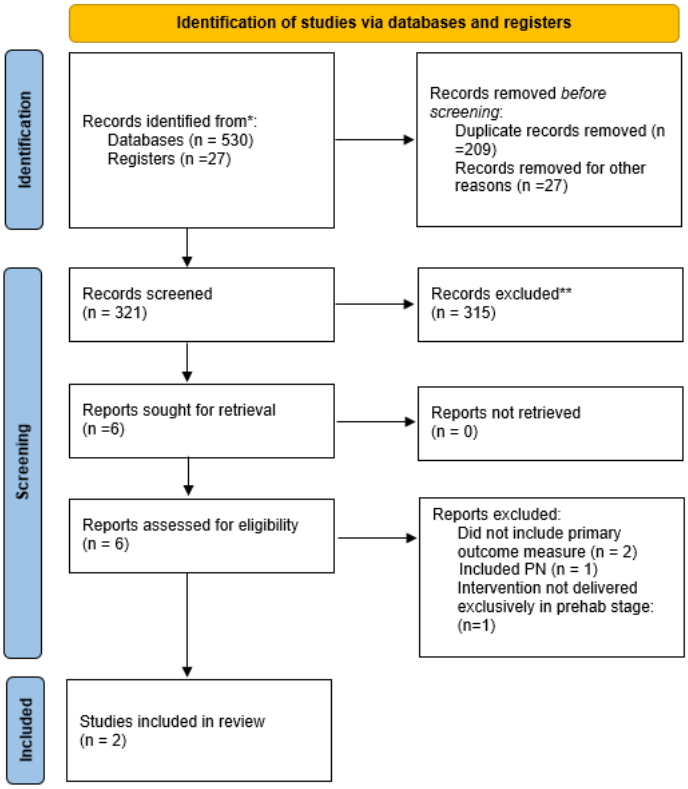

Figure 1

PRISMA flow diagram for systematic reviews.

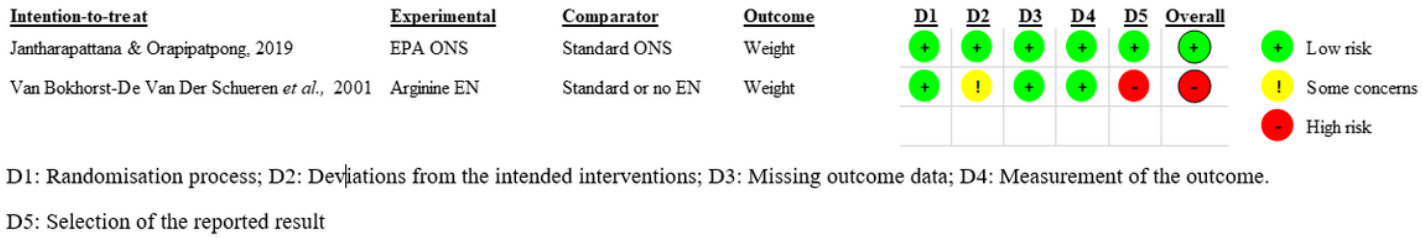

Figure 2

Traffic Light Plot of ROB 2 assessment

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