Nutritional prehabilitation in head and neck cancer: a systematic review

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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 outcome 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.

Keywords Head and neck cancer · Prehabilitation · Nutrition support · Weight loss

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, and 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 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 postoperative 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?

4) 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 7 and 10th May 2021 within Medline (including PubMed), CINHAL, Cochrane database, EMBASE, and ProQUEST. Clinical trial 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 was 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 PICO§s (Population, Intervention, Comparison, Outcome, Study type) and are outlined in Table 1.

**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 and 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 sec-
ondary reviewer and eligibility was agreed with no dis-
crepancies 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 was not 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
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 compo-
sition, 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 interven-
tion?

Table 1  The PICO characteristics for inclusion and exclusion of studies

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

#### Study selection

The primary literature search identified 530 articles from the database search of which 209 duplicates were removed. A search of clinical trial 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 (Fig. 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 $\geq 2$ 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 $n = 111$.

![Identification of studies via databases and registers](image_url)
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 and 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 were 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 interventions. Jantharapattana and 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 preoperative 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. Postoperatively, 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 7–10 days [38] (Table 4) with a low attrition rate reported across both studies.

Quality/risk of bias

Risk of bias is summarised in Fig. 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 postoperatively and on discharge; however, these data are unpublished. Jantharapattana and Orapipatpong [37] were identified in all domains and overall, as low risk of bias.

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 7–10-day period.
### 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/m² mean (±SD) | Handgrip strength, kg, mean (±SD) | Energy intake, kcal, mean | Lean body mass, mean (±SD) | Fat mass, mean (±SD) |
|--------|----------------|-------------|---------------------|--------------------|-----------------------------|----------------------|----------------------------------|--------------------------|--------------------------|----------------------|
| Jantharapattana and Orapipatpong, 2019 |  |  |  |  |  |  |  |  |  |  |
| G1: | 55.2 (13.5) | I: 24 (77.4) | T1, 2 (6.5); T2, 10 (32.3); T3, 4 (12.9); T4a, 14 (45.2); T4b, 1 (3.2) | I: Oral, 20 (64.5); Larynx, 5 (16.1); Oropharynx, 6 (19.4%) | I: 58 kg * | I: 22.3 (2.8) | Not measured | I: 1700** |  |
| G2: | 59.5 (13.4) | C: 26 (83.9) | C: T1, 5 (16.1); T2, 5 (16.1); T3, 5 (16.1); T4a, 15 (48.4); T4b, 1 (3.2) | C: Oral, 16 (51.6); Larynx, 8 (25.8); Oropharynx, 4 (12.9); Hypopharynx, 2 (6.5); Unknown, 1 (3.2) | C: 59 kg | C: 21.2 (3.6) |  |  |  |
| Van Bokhorst-De Van Der Schueren et al., 2001 |  |  |  |  |  |  |  |  |  |  |
| G1: | 55 (10) | G1: | T2, 3 (11.8); T4a, 11 (64.7); T4b, 1 (5.9); Recurrent, 3 (17.6) | G1: Oral, 5 (29.4); Larynx, 3 (17.6); Oropharynx, 5 (29.4); Hypopharynx, 4 (23.5) | G1: 62.8 (8.4) | Not measured |  |  | G1: 12.2 kg (16.8) |  |
| G2: | 60 (8) | G2: | T3, 2 (13.3); T4a, 7 (46.7); Recurrent, 5 (33.3); Not stage, 1 (6.7) | G2: Oral, 2 (13.3); Larynx, 3 (20); Oropharynx, 4 (26.7); Hypopharynx, 5 (33.3); Other, 1 (6.7) | G2: 55.3 (8.1) |  |  |  | G2: 36.3 kg (17.0) |  |
| G3: | 59 (12) | G3: | T3, 3 (17.6); T4a, 9 (52.9); Recurrent, 5 (29.4) | G3: Oral, 1 (5.9); Larynx, 3 (17.6); Oropharynx, 9 (32.9); Hypopharynx, 3 (17.6); Other, 1 (5.9) | G3: 61.6 (8.5) |  |  |  | G3: 13.0 kg (5.8) |  |
| G1: | 58.8 kg | G1: | T1, 1, 2 (6.5); T2, 10 (32.3); T3, 4 (12.9); T4a, 14 (45.2); T4b, 1 (3.2) | G1: Oral, 20 (64.5); Larynx, 5 (16.1); Oropharynx, 6 (19.4%) | G1: 58 kg | G1: 22.3 (2.8) | Not measured | G1: 1700** |  |
| G2: | 58.5 kg | G2: | C: T1, 5 (16.1); T2, 5 (16.1); T3, 5 (16.1); T4a, 15 (48.4); T4b, 1 (3.2) | C: Oral, 16 (51.6); Larynx, 8 (25.8); Oropharynx, 4 (12.9); Hypopharynx, 2 (6.5); Unknown, 1 (3.2) | C: 59 kg | C: 21.2 (3.6) |  |  | C: 41.1% (9) |  |
| G3: | 59.0 kg | G3: | T3, 3 (17.6); T4a, 9 (52.9); Recurrent, 5 (29.4) | G3: Oral, 1 (5.9); Larynx, 3 (17.6); Oropharynx, 9 (32.9); Hypopharynx, 3 (17.6); Other, 1 (5.9) | G3: 61.6 (8.5) |  |  |  | C: 25.6% (8.9) |  |

*Estimated value extracted from Fig. 3 in Jantharapattana and Orapipatpong [37]

**Estimated value extracted from Fig. 2 in Jantharapattana and Orapipatpong [37]
of preoperative intervention (Table 5). At 4-month follow-up, Jantharapattana and 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 postoperative complications and LOS between groups in both studies (Table 5). Neither study collected any QOL patient-reported outcome measures for synthesis or discussion.

The components of the nutritional and other prehabilitation interventions

Both studies investigated the use of an “enriched” nutritional formula. Jantharapattana and Orapipatpong [37] used an ONS which contained 2.2 g 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, 7–10 days. Preoperative tube feeding was provided for $8.8 \pm 1.4$ days (group 2) and $8.6 \pm 1.4$ days (group 3) [38], while the oral nutritional supplements were reported to have been consumed for at least 7 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 were 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 dietician; however, the details of the purpose of the call or advice provided were 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 and 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 (1750 kcal at baseline; 2300 kcal at 21 days) and control groups (1800 kcal at baseline; 2350 kcal at 21 days).

Participants in the study by Van Bokhorst-De Van Der Schueren et al. [38] maintained enteral feeding for $8.8 \pm 1.4$ days (group 2) and $8.6 \pm 1.4$ 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
Table 4: Intervention characteristics of the included studies according to TIDieR checklist

| Study                                                                 | Intervention name                                      | Comparison Why | What (material) | What (procedure) | Who provided | How (mode of delivery) | Where | When and how much | Tailoring | Modification | How well (planned) | How well (actual) |
|----------------------------------------------------------------------|--------------------------------------------------------|----------------|----------------|-----------------|--------------|------------------------|-------|-------------------|-----------|--------------|-------------------|------------------|
| Jantharapatanata and Orapi-patpong, 2019                            | Efficacy of preoperative EPA-enriched ONS in HNC      | 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 Netherlands) | 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 at home. | ONS consumed preoperatively at home. Face to face appointment to obtain baseline data, biochemistry and complete history taking. | Postoperative supplements were consumed in hospital. | None reported | The volume of ONS consumed was recorded in a diary. |
| Van Bokhorst-De Van Der Schueren et al., 2001                       | Perioperative arginine enriched enteral feeding in HNC | 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 | 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 at home. 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. Postoperative EN was taken in the hospital. | For 7–10 days pre surgery to meet EER: G3: enriched EN formula (41% of casein was replaced with arginine). G2: isocaloric and isonitrogenous standard formula. | None reported | Nutritional intake was recorded in a diary. |

G1: group one, no perioperative nutrition support; G2: group two, standard perioperative 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.
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 was effective at improving nutritional status or functional outcomes when provided for 7–10 days preoperatively. Jantharapattana and Orapipatpong [37] presented 4-month follow-up data on weight loss. Weight loss in both intervention and control groups was minimised to 5%, 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 postoperative 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-existing 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 and 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 and 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 25–30 kcal/kg/day and protein requirements at least 1.2–1.5 g/kg/day of body weight [46–48]. Indeed, some studies suggest that energy and protein requirements for HNC patients undergoing treatment are 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 among 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 7-day prehabilitation study in a mixed cohort of abdominal and

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**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, days | Survival |
|-------------------------------|---------------------------------------|-------------------------------|-----------------------------------------------|--------------|--------------------------------|---------------------|----------|
| **Jantharapattana and 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% | | Not measured | **Change in mean calorie intake** Preoperatively, day 1–7: I: 50 kcal C: 100 kcal At 21 days: I: 550 kcal C: 550 kcal | 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: 1.3 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) G2: 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) |

*Estimated value extracted from figure 3 in Jantharapattana & Orapipatpong [37]
**Estimated value extracted from figure 2 in Jantharapattana & Orapipatpong [37]
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 (280 kcal, 26 g protein/250 ml 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 postoperative mobility and decreased incidence of pulmonary morbidity were demonstrated in prehabilitation versus no prehabilitation group. No differences in overall infections, LOS, or hospital readmission were 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 were 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 is 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 would not have impacted the results. A strength however is that all studies that met the inclusion criteria were included; none was 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.

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

Code availability Not applicable as no software of coding was used.

Declarations

Ethical approval This is a systematic review. No ethical approval required.

Consent to participate Not applicable as there were no human subjects.

Consent for publication Not applicable.

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