



Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: <http://www.clinicalnutritionespen.com>

Meta-analysis

The effect of timing of enteral nutrition support on feeding outcomes and dysphagia in patients with head and neck cancer undergoing radiotherapy or chemoradiotherapy: A systematic review

Xiaodan Ye ^{a,*}, Yuan-Chin Chang ^a, Merran Findlay ^{b,c}, Teresa Brown ^{a,d}, Judy Bauer ^a^a School of Human Movement and Nutrition Sciences, University of Queensland, Queensland, Australia^b Cancer Services, Royal Prince Alfred Hospital, New South Wales, Australia^c Chris O'Brien Lifehouse, New South Wales, Australia^d Nutrition & Dietetics, Royal Brisbane & Women's Hospital, Queensland, Australia

ARTICLE INFO

Article history:

Received 13 January 2021

Accepted 17 May 2021

Keywords:

Head and neck neoplasms

Enteral feeding

Gastrostomy

Nasogastric intubation

Radiotherapy

Chemoradiotherapy

SUMMARY

Background & aims: Patients with head and neck cancer (HNC) often require enteral nutrition (EN). This systematic review reports the effect of EN timing in patients with HNC undergoing curative-intent and definitive or adjuvant radiotherapy or chemoradiotherapy on tube feeding duration, tube-related complications and dysphagia.

Methods: Randomised controlled trials (RCTs) published between January 2015–April 2020 were obtained from Medline, CINAHL and Embase. Study quality and certainty of evidence were assessed with Cochrane Risk-of-Bias and Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results: Two RCTs (n = 265) in five manuscripts were included. The risk of bias was moderate in one RCT and low in the other RCT. Timing of EN (prophylactic vs. reactive) may have little or no effect on tube feeding duration or complications, however, the effect on dysphagia was uncertain. Certainty of evidence was low for short-term and moderate for long-term tube feeding duration, low for tube-related complications and very low for dysphagia. There was imprecision due to small sample sizes, heterogeneity in the definitions and protocols for prophylactic and reactive EN, variations in time points for outcome assessment and indirect dysphagia measures.

Conclusion: Larger well-designed trials are warranted to increase certainty of evidence regarding EN timing in patients with HNC.

© 2021 European Society for Clinical Nutrition and Metabolism. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Head and neck cancer (HNC) is one of the most common types of cancer worldwide and is strongly associated with alcohol and tobacco consumption [1], human papillomavirus (HPV) infection and Epstein–Barr virus (EBV) [2]. Over the last 50 years, HNC caused by HPV infection is increasing [3], accounting for 60–70% of all oropharyngeal cancers diagnosed in Australia [4]. Patients with HNC who undergo treatments including radiotherapy (RT) and chemoradiotherapy (CRT) of curative-intent often experience severe nutrition-impact symptoms and side effects, including

trismus, xerostomia, dysphagia and odynophagia, which can adversely compromise oral intake [5] and unintentional weight loss and malnutrition are likely to occur [6]. As a result, adequate nutrition is crucial during cancer treatment to maintain nutritional status, quality of life (QoL), immune function and physical function, and to reduce the risk of unplanned hospital admissions and mortality [7]. In this situation, enteral nutrition (EN) is indicated and can be provided through a nasogastric tube (NGT) when EN is only needed short-term (<four weeks), or gastrostomy tube (GT) when medium to longer term EN is required [8]. Types of GT include percutaneous endoscopic gastrostomy (PEG),

* Corresponding author. School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Queensland, 4072, Australia.

E-mail addresses: x.ye@uqconnect.edu.au (X. Ye), yuanchin.chang@uqconnect.edu.au (Y.-C. Chang), merran.findlay@health.nsw.gov.au (M. Findlay), Teresa.Brown@health.qld.gov.au (T. Brown), j.bauer1@uq.edu.au (J. Bauer).

radiologically-inserted gastrostomy (RIG) and surgically-inserted gastrostomy [8]. The placement of an enteral feeding tube is generally safe with a low complication rate for both routes of tube insertion [9–11].

The optimal timing of feeding tube placement and enteral feeding commencement among patients with HNC has been an ongoing debate [12]. They can be either placed prophylactically prior to treatment commencement, and/or used for prophylactic feeding during treatment [13]; or placed reactively, following clinical indications after treatment initiation; with protocols varying between centres [14]. Previous systematic reviews and Internationally endorsed evidence-based guidelines for the nutritional management of adult patients with HNC have recommended a prophylactic approach to GT placement and commencement of enteral feeding to improve nutritional outcomes [14–19].

Some studies have shown that prophylactic EN can improve QoL and nutrition status through maintaining body weight and reducing the risk of malnutrition [17,20]. Other studies suggested that prophylactic EN may negatively affect QoL due to social isolation and prolonged tube dependency [21]. This highlights that whilst QoL and nutrition status are critical aspects to consider when providing nutrition support to patients with HNC, the relevance of tube dependency should not be disregarded. Tube dependency was not clearly defined in previous systematic reviews [22,23]. Additionally, these studies did not specify the time period required to be considered as tube dependent, nor the contributing factors for tube dependency. It was assumed that the presence of the tube led to dependency but this may not be the case [24].

Dysphagia is another complex clinical problem associated with treatment of HNC characterised by difficulty swallowing, and is a well-documented consequence of RT and CRT [25] and a predictor for tube feeding [22]. It requires close monitoring to prevent choking and chronic aspiration [25]. The Shaw et al. [7] systematic review reported inconsistent results for dysphagia.

The current evidence demonstrates a lack of consensus and limited certainty of evidence due to the inclusion of a high proportion of non-randomised studies in previous systematic reviews. The aim of this systematic review was to investigate the effect of timing of EN on tube feeding duration, tube-related complications and dysphagia in patients with HNC undergoing curative-intent RT or CRT in definitive or adjuvant settings, evaluating the hierarchy of evidence from RCTs only.

2. Materials & methods

2.1. Protocol registration

This review was undertaken and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework [26] and was registered with PROSPERO, an International prospective register of systematic reviews (Registration no. CRD42020178704) on 5 July 2020.

2.2. Eligibility criteria

Publications were eligible for inclusion if they met the following criteria: 1) Participants diagnosed with HNC were ≥ 18 years and underwent treatment with curative-intent; 2) Employed either definitive or adjuvant RT or CRT; 3) Compared one or more enteral feeding methods differing by timing of EN between the intervention and control groups; 4) Included $\geq$ one of the outcomes of interest: tube feeding duration, tube-related complications or dysphagia; and 5) Were RCTs published in English-language peer-reviewed journals. Conference abstracts, case studies and literature reviews were excluded.

2.3. Search strategy

A literature search was conducted in three electronic databases including Medline, EMBASE and CINAHL to obtain relevant publications published between January 2015 and April 2020. Additional publications were retrieved from reference lists of identified systematic reviews with no publication date restrictions.

The search strategy included keywords and MeSH headings: ('head and neck neoplasm*', 'head and neck cancer') combined using the Boolean operator AND with (gastrostom*, 'enteral nutrition', 'tube feeding', 'force feeding', 'PEG tube', 'G-tube', 'enter* feeding', 'gastric feeding tube') and ('treatment outcome', 'quality of life', 'dependence*', 'dysphagia', 'weight', 'body mass index')

A summary of the search strategy conducted in EMBASE is provided in [Supplementary Table 1](#).

2.4. Data extraction

Two authors (XY and YC) independently reviewed the manuscripts against the eligibility criteria and quality assessment tools. Any discrepancies were resolved by consensus upon discussion with another co-author (JB).

A data extraction table ([Table 1](#)) was compiled to record study characteristics and participant characteristics including age, gender, cancer site and cancer stages. Results were synthesised by each outcome of interest: tube feeding duration, tube-related complications and dysphagia.

Due to a repetition of results reported across the included manuscripts of the same RCT, a priority will be placed on sources that included all participants in analysis and/or had the longest follow up.

2.5. Quality assessment

The quality of the included RCTs was assessed using the Cochrane Risk-of-Bias tool for randomised trials Version 2 (RoB2) [31]. Five domains of the RCTs were assessed: the randomisation process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and the selection of the reported result [31]. Two authors (XY and YC) independently assessed and assigned a grade of "low", "some concerns" or "high" risk of bias to each study. Any judgement differences were resolved by consensus through discussion with other co-authors (MF, TB and JB).

The certainty of evidence was determined by two authors (XY and YC) using the online Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [32] based on study designs, risk of bias, inconsistency, indirectness, the imprecision of results and other considerations including publication bias, large effect, plausible confounding and dose–response gradient.

Due to heterogeneity amongst the studies in patient characteristics, protocols of prophylactic and reactive EN and definitions of tube-related complications, a meta-analysis was unable to be performed. Thus, a narrative summary of results was reported here.

2.6. Prophylactic and reactive enteral nutrition support definition

Protocols of prophylactic and reactive EN support for the different RCTs are presented in [Table 2](#). In this systematic review, pPEG is defined as PEG tube inserted prophylactically [13,27–30] and EN regimen initiated immediately post-insertion [29,30] or when oral intake became inadequate and weight loss >1 kg [13,27,28]. Reactive tube feeding will be defined as PEG (rPEG) or NG (rNGT) tube inserted either prophylactically but EN regimen initiated only when clinically indicated [29,30] or inserted reactively for immediate use [13,27,28].

Table 1

Summary of patient's baseline characteristics of the two included RCTs.

Author, year	Country	Sample size	Gender, N (%)	Age, years (Mean $\pm$ S.D) or (median [range])	Cancer site, N (%)	Tumour stage, N (%)	TNM Staging, N (%)
1 RCT reported in 3 manuscripts: Silander et al. [13]; Silander et al. [27]; Axelsson et al. [28].	Sweden	134	T (pPEG): M: 43 (67) F: 21 (33) C (rPEG/rNGT): M: 48 (69) F: 22 (31)	T (pPEG): 63 [41–87] C (rPEG/rNGT): 60 [35–83]	T (pPEG): Oropharynx = 37 (58) Oral cavity = 22 (34) UKP = 3 (5) Hypopharynx = 2 (3) Nasopharynx = 0 C (rPEG/rNGT): Oropharynx = 41 (58) Oral cavity = 20 (29) UKP = 7 (10) Hypopharynx = 0 Nasopharynx = 2 (3)	T (pPEG): III: 16 (25) IV: 48 (75) C (rPEG/rNGT): III: 18 (26) IV: 52 (74)	T (pPEG): T1: 9 (14) T2: 17 (27) T3: 10 (16) T4: 24 (38) T0: 3 (5) N-Positive: 47 (73) C (rPEG/rNGT): T1: 8 (11) T2: 16 (23) T3: 11 (16) T4: 28 (40) T0: 7 (10) N-Positive: 54 (77)
1 RCT reported in 2 manuscripts: Brown et al. [29] & Brown et al. [30]	Australia	131	T (pPEG): M: 56 (92) F: 5 (8) C (rPEG): M: 59 (84) F: 11 (16)	T (pPEG): 61.1 $\pm$ 9.1 C (rPEG): 60.0 $\pm$ 10.9	T (pPEG): Oral cavity: 7 (11) Oropharynx: 45 (74) Nasopharynx: 2 (3) Hypopharynx: 5 (8) Larynx: 1 (2) UKP: 1 (2) Other: 0 (0) C (rPEG): Oral cavity: 7 (10) Oropharynx: 56 (80) Nasopharynx: 2 (3) Hypopharynx: 3 (4) Larynx: 1 (1) UKP: 0 (0) Other: 1 (1)	T (pPEG): II: 0 (0) III: 5 (9) IV: 52 (91) C (rPEG): II: 1 (1) III: 10 (15) IV: 56 (84)	T stage T (pPEG): T0: 1 (2) T1: 4 (7) T2: 24 (39) T3: 11 (18) T4: 21 (34) C (rPEG): T0: 0 (0) T1: 4 (5) T2: 20 (29) T3: 26 (37) T4: 20 (29) N stage T (pPEG): N0: 5 (8) N1: 5 (8) N2a: 3 (5) N2b: 25 (41) N2c: 22 (36) N3: 1 (2) C (rPEG): N0: 7 (10) N1: 8 (11) N2a: 1 (1) N2b: 30 (43) N2c: 20 (29) N3: 4 (6)

Abbreviations: C, Control group; pPEG, Prophylactic Percutaneous Endoscopic Gastrostomy; RCT, Randomised Controlled Trial; rPEG, Reactive Percutaneous Endoscopic Gastrostomy; rNGT, Reactive Nasogastric Tube; T, Treatment group; TNM, Tumour, Node, Metastasis; UKP, Unknown Primary.

Table 2

Definitions of pPEG and rPEG and/or/rNGT placement and feeding.

RCT, Author (Year)	pPEG	rPEG and/or rNGT
1 RCT reported in Silander et al. [13], Silander et al. [27], Axelsson et al. [28]	Placement PEG placed prior to treatment initiation. Feeding Commenced in an average of 31 days into treatment, initiated when oral intake became inadequate and weight loss >1 kg.	Placement PEG/NGT placed during treatment, following clinical indications. Feeding Commenced in an average of 54 days into treatment, feeding commenced when clinically indicated.
1 RCT reported in Brown et al. [29], Brown et al. [30]	Placement PEG placed prior to treatment initiation. Feeding Enteral feeding initiated immediately following placement.	Placement PEG placed prophylactically prior to treatment initiation. Feeding The clinical criteria of feeding commencement included: meeting <60% of estimated energy requirement for >10 days; difficulty in maintaining weight; patient required significant texture modified diet; increased or uncontrolled nutrition impact symptoms. 50% of participants commenced on average 21 days into treatment.

Abbreviations: NGT, Nasogastric Tube; pPEG, Prophylactic Percutaneous Endoscopic Gastrostomy; RCT, Randomised Controlled Trial; rPEG, Reactive Percutaneous Endoscopic Gastrostomy; rNGT, Reactive Nasogastric Tube.

2.7. Tube feeding duration definition

Tube feeding duration was defined as the number of days a patient required EN, from the start of enteral feeding to tube removal [13,28] or from treatment completion to tube removal [29,30]. The term “tube dependency” has been used to describe the duration of enteral feeding [13,28–30], however, the term was not well-defined. For the purpose of this systematic review, the term “tube feeding duration” will replace tube dependency and is defined as the length of time an individual received EN support.

2.8. Major and minor complication definition

Only Brown et al. [29,30] defined and classified major and minor tube-related complications. To ensure consistency, this systematic review will consider major complications as those requiring hospital admission for management [27]; while minor complications are those that could be managed with minimal interventions

including oral antibiotics for site infections or other stoma issues such as hyper-granulation, excoriation, erythema, pressure injury, leakage, and feeding tube dislodgement [13,29,30].

3. Results

A total of 1536 publications were identified via electronic databases. One additional publication that was known to the authors was included and four additional publications were identified through hand-searching the reference lists. After screening the titles, abstracts and full texts, five manuscripts that met the inclusion criteria were included for analysis, with reasons for exclusion outlined in Fig. 1 [26].

3.1. Study characteristics

Two RCTs were reported in five included manuscripts. Study populations included adults (≥ 18 years) with any types of head and

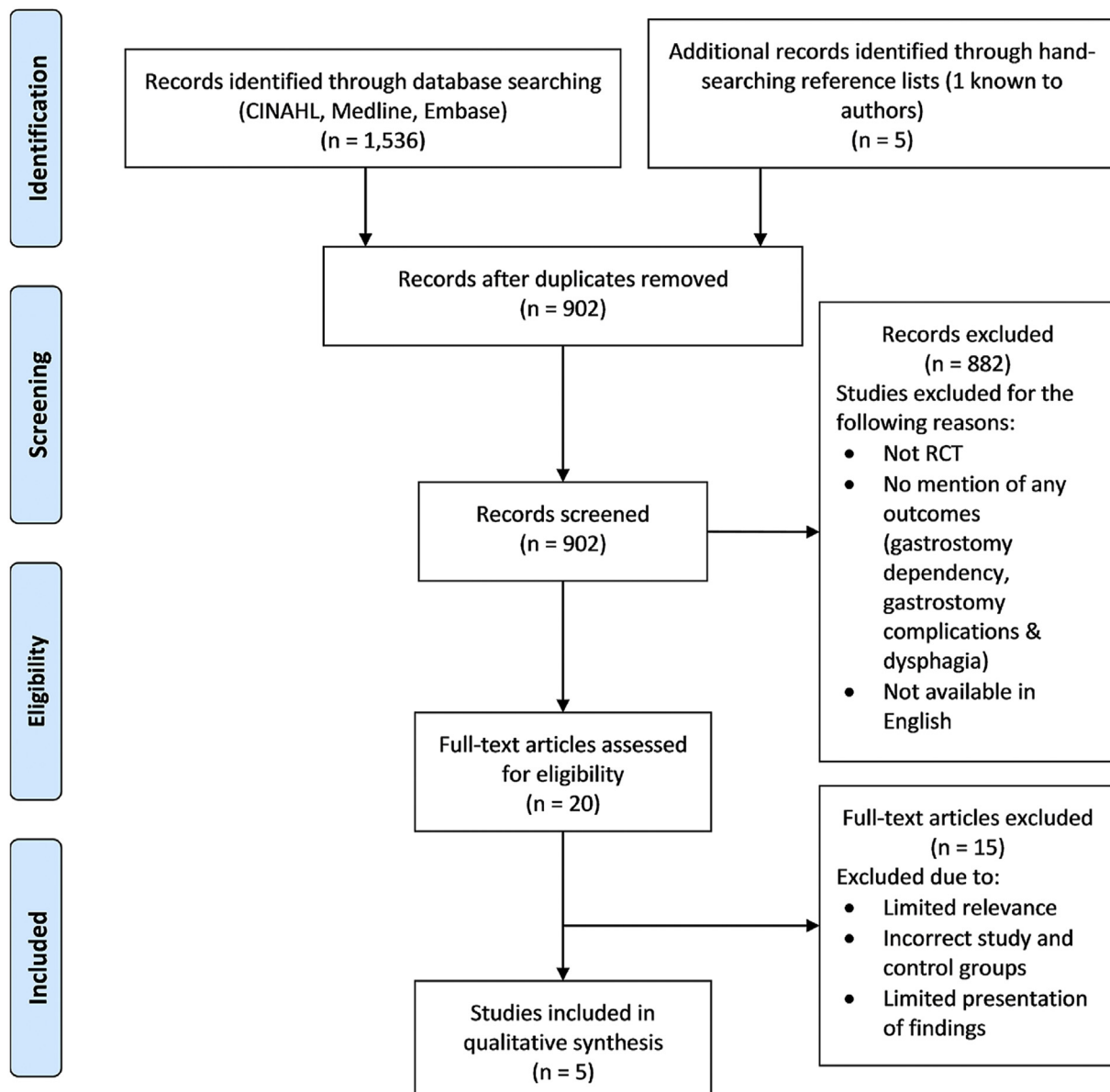


Fig. 1. PRISMA flow diagram showing study selection process according to PRISMA guidelines. Abbreviations: RCT, Randomised Controlled Trial.

neck squamous cell carcinoma and in any tumour stages. Sample size ($n = 265$) ranged from 131 [29,30] to 134 [13,27,28] participants. The RCTs were conducted in Sweden ($n = 1$) [13,27,28] and Australia ($n = 1$) [29,30]. Characteristics and results of the included studies were summarised in Tables 1 and 3 respectively.

Follow-up assessment occurred during and post-treatment in Silander et al. [13,27] and Axelsson et al. [28], but only post-treatment in Brown et al. [29,30]. The RCT by Brown et al. compared nutritional, clinical and patient outcomes in one

manuscript [29], and the long-term impact of prophylactic enteral feeding on outcomes was assessed in another manuscript [30]. The second RCT was reported in three manuscripts by Silander et al. [13,27] and Axelsson et al. [28]. The first manuscript examined the impact of early tube feeding on malnutrition risk, quality of life and energy intake [27], the second manuscript investigated hospital admissions and quality of life [13] and the third manuscript assessed the long-term effects of tube feeding on dysphagia severity up to ten years [28].

Table 3

Summary of study descriptive and key findings for the two randomised controlled trials in the systematic review.

Author, year	Sample Size (N)	Outcome	Results
1 RCT reported in 3 manuscripts: Silander et al. [13]; Silander et al. [27]; Axelsson et al. [28].	pPEG (N = 64) rPEG/rNGT (N = 70) rPEG: 6 rNGT: 45 Nil EN: 19	Tube feeding duration	Silander et al., [13] • Use of EN: pPEG 98% vs. rPEG/rNGT 90% • Mean days of tube use: pPEG 177 days vs. rPEG/rNGT 122 days ($P < 0.0001$) • In patients who have used EN ($N = 115$), mean days of tube use: pPEG 180 days vs. rPEG/rNGT 160 days ($P = 0.0276$) ◦ RT and surgery: pPEG 182 days vs. 92 days rPEG/rNGT ($P = NS$) ◦ CRT: pPEG 182 days vs. rPEG/rNGT 170 days ($P = 0.043$) ◦ CRT and surgery: pPEG 181 days vs. rPEG/rNGT 221 days ($P = NS$) Silander et al., [27] – Not reported Axelsson et al., [28]
		Tube-related complications	• Use of EN: 7% after 12 months, 2% after 24 months and 0% after 8 years. Silander et al., [13] • Serious complications: pPEG 1 vs rNGT 0 ($P = NS$) • Most common PEG-site complication: granulation tissue around the stoma and peristomal infection. • rNGT group: ◦ Unintentional NGT dislocation ($N = 28$): On 2–4 occasions ($N = 19$) and on 7 occasions ($N = 1$). ◦ Mild side effects ($N = 15$; i.e., tube-blocking) Silander et al., [27] – Not reported Axelsson et al., [28] – Not reported
		Dysphagia	Silander et al., [13] - EORTC QLQ HN35 • Mean swallowing scale pPEG vs. rPEG/rNGT ◦ Baseline: 12 vs. 19 ($P = NS$) ◦ After 3 months: 55 vs. 58 ($P = NS$) ◦ After 6 months: 29 vs. 34 ($P = NS$) Silander et al., [27] - EORTC QLQ C30 & EORTC QLQ HN35 • Mean swallowing scale presented in graphical diagrams. ◦ Baseline vs. 2–3 months: Clinically important increase (>20 points) in difficulty with swallowing solid food, pureed food and liquid in both groups. ◦ 2–3 months to six months: Clinically important in difficulty with swallowing solid food, pureed food and liquid. ◦ Six months to 24 months: no significant decrease in swallowing score of solid food, pureed food and liquid. ◦ Choking with swallowing remained consistent at two, three, six, 12 and 24 months. Axelsson et al., [28] - EORTC QLQ HN35 • Mean swallowing scale pPEG vs. rPEG/rNGT ◦ After 24 months: 19 vs. 21 ($P = 0.88$) ◦ After 8 years: 21 vs. 18 ($P = 0.97$) • No significant difference at any timepoint for swallowing. Brown et al. [30],
1 RCT reported in 2 manuscripts: Brown et al. [29] & Brown et al. [30]	pPEG (N = 61) rPEG (N = 70)	Tube feeding duration	• Median (range) time to tube removal: pPEG 100 days (28–276) vs. rPEG 110 days (21–280) ($P = 0.339$). • Rate of gastrostomy use at 12 months post-treatment: 4% for both groups. Brown et al. [29],
		Tube-related complications	• Average use of tube: pPEG 115.5 days vs. rPEG 104.7 days ($P = 0.333$). Brown et al. [30], • At 3-months post tube insertion: ◦ Major tube complications: pPEG 11% vs. rPEG 10% ($P = 0.989$). ◦ Minor tube complications: 40% in both groups ($P = 0.995$). ◦ $N = 27/50$ of the minor complications were site infections. Brown et al. [29],

Table 3 (continued)

Author, year	Sample Size (N)	Outcome	Results
		Dysphagia	- At 3-months post tube insertion: - No gastrostomy placement-associated mortality in both groups. Brown et al. [30] - Diet texture - Baseline: pPEG 69% vs. rPEG 67% were on full diet ($P = 0.778$). - After 3 months: pPEG 53% vs. rPEG 51% were on full diet ($P = 0.727$). Brown et al., [29] - EORTC QLQ HN35 - Change of swallowing scale from baseline to 3 months: pPEG 6.2 ± 22.5 vs. rPEG 8.8 ± 28.1 ($P = 0.564$) - No significant effects found following adjustment for other confounding variables

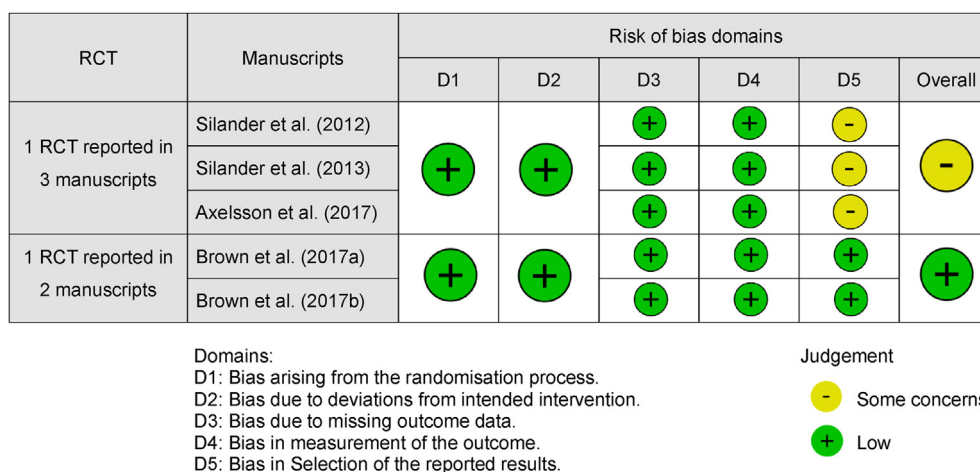
Abbreviations: CRT, Chemoradiotherapy; EORTC QLQ C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ HN35, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Head & Neck Cancer 35; EN, Enteral Nutrition; NGT, Nasogastric Tube; PEG, Percutaneous Endoscopic Gastrostomy; pPEG, prophylactic Percutaneous Endoscopic Gastrostomy; RCT, Randomised Controlled Trial; rPEG, reactive Percutaneous Endoscopic Gastrostomy; rNGT, reactive Nasogastric Tube; RT, Radiotherapy.

3.2. Study quality and certainty of evidence (GRADE)

When rated using RoB2, the RCT reported in Silander et al. [13,27], and Axelsson et al. [28] was downgraded to “moderate risk” related to the measurement of the outcome and selection of the reported result. The RCT reported in Brown et al. [29,30] was rated

“low risk”. A *robvis* plot was created to visualise the results from the risk of bias assessment (Fig. 2) [33].

Certainty of evidence for each outcome based on GRADE is presented in Table 4. It was rated very low for short term (<12 months) and moderate for long term (≥ 12 months) tube feeding duration, low for tube-related complications and very low for dysphagia.

**Fig. 2.** Robvis plot showing risk of bias of RCTs per RoB2 domain.**Table 4**

Certainty of evidence assessed using GRADE.

Certainty assessment							Certainty	Importance
No. of RCTs	Study design (No. Of manuscripts)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
2 [13,28–30]	Tube feeding duration – Short-term (<12 months) RCT (reported in 4 manuscripts)	serious ^a	serious ^b	not serious	serious ^d	none	⊕○○○ VERY LOW	Important
2 [28,30]	Tube feeding duration – Long term (≥ 12 months) RCT (reported in 2 manuscripts)	not serious	not serious	not serious	serious ^d	none	⊕⊕⊕○ MODERATE	Important
2 [13,29,30]	Tube-related complications RCT (reported in 3 manuscripts)	serious ^a	not serious	not serious	serious ^d	none	⊕⊕○○ LOW	Important
2 [13,27–30]	Dysphagia RCT (reported in 5 manuscripts)	serious ^a	not serious	serious ^c	serious ^d	none	⊕○○○ VERY LOW	Important

^a Risk of bias assessed using RoB2. Axelsson et al. [28] Silander et al. [13] & Silander et al. [27]: some concerns with participants, carers and outcome assessors knowing the intervention assigned to with nil information regarding trial deviation. Brown et al. [29] & Brown et al. [30]: Low concerns.

^b Variations in the protocols and definitions of prophylactic and reactive EN used between the trials.

^c Indirect measures of dysphagia using diet texture.

^d Sample size <400 but >100, and no analysis for precision (e.g. 95% confidence level) was done.

3.3. Tube feeding duration

The two RCTs reported in four manuscripts examined the effect of timing on tube feeding duration, one [29,30] was rated “low risk” and the other [13,28] was rated “moderate risk” of bias. Inconsistent results were found at short-term (<12 months) follow up and no significant difference was found at long-term (≥ 12 months) follow up. Certainty of evidence was assessed as very low for short-term tube feeding duration and was downgraded due to serious risk of bias, inconsistency and imprecision, and moderate for long-term tube feeding duration, downgraded for imprecision.

Tube feeding duration was measured at short-term follow up (<12 months) [13,29,30]. Silander et al. [13] found that the mean tube feeding duration from start of tube feeding to removal was significantly longer in the pPEG compared to the rPEG/rNGT group (177 vs. 122 days, $p < 0.0001$). A significant difference was also found when considering only patients who used enteral feeding during tumour treatment (pPEG 180 vs. rPEG/rNGT 160 days, $p = 0.0276$). In contrast, Brown et al. reported no significant difference in the mean time to tube removal between the pPEG and rPEG group (115.5 vs. 104.7 days, $p = 0.333$) [29], and median [range] time to tube removal (pPEG 100 [28–276] vs. rPEG 110 days [21–280], $p = 0.339$) [30].

The percentage of patients requiring enteral feeding was investigated at long-term follow up (≥ 12 months) in the two RCTs included [28,30] with no significant differences between the groups. Brown et al. [30] reported at 12-months post-treatment, the percentage of patients remaining on tube feeding was low in both groups (4%), and was due to postoperative functional dysphagia (3%) or severe dysphagia following definitive CRT (1%). Axelsson et al. [28] followed 108 patients for up to ten years and found no significant difference in both groups at 12 months (7%), 24 months (2%) and 8 years (0%).

3.4. Tube-related complications

Certainty of evidence was assessed as low for tube-related complications and was downgraded due to serious risk of bias and imprecision. The two RCTs reported in three manuscripts examined EN timing and tube-related complications, with one RCT [29,30] rated “low risk” and the another [13] rated “moderate risk” of bias. No significant difference was found in minor or major tube-related complications among all studies investigated [13,29,30].

During the first three months post-PEG insertion, Brown et al. [29,30] reported no gastrostomy placement-associated mortality. Minor (40% vs. 40%) and major (11% vs. 10% [30]; 12% vs. 10% [29]) complication rates were similar between the pPEG and rPEG groups. Silander et al. [13] reported mild local infection as the most common minor complication in both pPEG/rPEG and rNGT groups. One major complication was found in a patient with pPEG, who experienced peritonitis and general organ failure six days after tube dislodgement when the patient had delirium tremens [13]. No patients in the rNGT group experienced major complications.

3.5. Dysphagia

The two included RCTs reported in five manuscripts examined EN timing and dysphagia [13,27–30]. One RCT [29,30] was rated “low risk” and the other [13,27,28] was rated “moderate risk” of bias. Certainty of evidence was rated very low for dysphagia and was downgraded due to serious risk of bias, indirectness and imprecision. Two different indirect assessment tools were used across the studies and all reported no significant difference in dysphagia between groups.

Both of the two RCTs [13,27–29] assessed dysphagia severity using the swallowing scale in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire in Head and Neck Cancer Patients-35 (EORTC QLQ HN35). Both RCTs suggested an increase in dysphagia short-term (<6 months). The RCT results reported in the manuscripts by Axelsson et al. [28], Silander et al. [13] and Silander et al. [27] suggested a clinically important increase in dysphagia severity from baseline to the third month follow-up after the start of treatment in both the pPEG and rPEG/rNGT groups. Whereas in Brown et al. [29], there was no significant change of swallowing scale from baseline to three months post-treatment between the groups. Only one RCT [13,27,28] assessed the impact of dysphagia after six months and found an insignificant reduction ($p > 0.05$). Swallowing returned to a level similar to baseline at two years and eight years after treatment initiation [28]. Despite a clinically important increase (≥ 10 points) in dysphagia scale in the short-term and a decline of swallowing problems over the long term, no statistically significant differences were found between the groups at any time points assessed.

Silander et al. [13] further separated the swallowing scale into four questions: problems with swallowing solid food, pureed food, liquids and choking with swallowing. Patients in both the pPEG and rPEG/rNGT groups showed a clinically important increase in difficulties eating solid foods, pureed foods and liquids from baseline to the third month follow-up [13]. The statistics were comparable when assessed at 12 months, 24 months and eight years after starting treatment [28]. There was an increased problem with choking when swallowing, which continued to be a significant issue after two years for both groups [27].

Dysphagia severity using diet texture was reported by Brown et al. [30], with 69% of patients in the pPEG and 67% in the rPEG group tolerating a full diet at baseline ($p = 0.778$). The remainder of patients were either on a soft, minced or pureed diet. At three months post-treatment, 51% of pPEG compared to 67% in the rPEG group returned to full diet ($p = 0.727$) [30]. It was also found that 5% of patients in each group were on a liquid diet, and 3% in the control group was nil by mouth [30].

4. Discussion

This is the first systematic review of RCTs exploring the impact of EN timing on tube feeding duration, tube-related complications and dysphagia in patients with HNC undergoing RT or CRT in definitive or adjuvant settings. Certainty of evidence was very low for short-term and moderate for long-term tube feeding duration, low for tube-related complications and very low for dysphagia. This was downgraded due to risk of bias (short-term tube feeding, tube-related complications and dysphagia), inconsistency (short-term tube feeding), imprecision due to small sample sizes (all outcomes) and indirectness (dysphagia).

EN timing may have little or no effect on short-term (<12 months) tube feeding duration [13,28–30]. One RCT [13,28] found patients with pPEG experience significantly longer tube feeding duration while the other RCT [29,30] found no significant difference. This may be related to different prophylactic and reactive EN protocols being used [13,28–30]. Participants in the pPEG group in both RCTs received PEG tubes prior to treatment and feeding initiated immediately after tube placement in Brown et al. [29,30], but an average of 31 days into treatment in Silander et al. and Axelsson et al. [13,28], which appeared to be more consistent with a reactive approach to Brown et al. [29,30]. Patients' nutritional status may have deteriorated at the point of receiving EN that they require longer EN support. However, it's unclear whether the increased duration in the pPEG group was attributed to the

difference in the timing of EN support commencement or tube placement.

At long-term follow ups (≥ 12 months), there was no difference in tube feeding duration between the two groups [28,30]. This disagrees with Wopken et al. [22], who concluded that patients with pPEG were more likely to retain their tube at both six- and 12-months post-treatment, or the inconclusive findings from Shaw et al. [7]. Nevertheless, longer duration of tube feeding may not necessarily be a negative outcome if patients clinically required EN to maintain or improve their nutritional status.

Tube feeding duration was measured at different timepoints across the RCTs, which prevented direct comparison and emphasises the need of similar measurement timepoints in future studies. One measured from the day of tube feeding commencement during treatment to tube removal [13,27], and another measured from the day of treatment completion to removal [29,30]. Most patients are likely to receive EN during treatment due to the tumour symptoms and treatment side effects. As there is an improvement to tumour symptoms and treatment side effects following treatment, measuring from treatment completion would provide a clearer picture on whether different timing of EN influenced tube feeding duration.

The overall minor and major complications rates were not significantly different between the pPEG and rPEG/rNGT groups and no PEG placement-associated mortality occurred in both groups [13,29,30]. This is consistent with Zhang et al. [18], which reported no significant difference in tube-related complication rate between pPEG and rPEG (RR: 1.35, 95% CI: 0.37–4.95).

Dysphagia was measured using EORTC-QLQ-HN35 and diet texture across the RCTs [13,27–30]. Although there was no difference in dysphagia between the groups, there is uncertainty with the effect of EN timing on dysphagia, which is consistent with Shaw et al. [7]. EORTC-QLQ-HN35 is a subjective measure assessing QoL associated with swallowing. The actual incidence of dysphagia may not be accurate due to reporting bias of the participants. Additionally, the frequency of long-term follow-up to examine the changes of swallowing outcomes overtime was limited, one RCT assessed dysphagia only once throughout the trial [29,30]. Follow-up timepoints were different across the RCTs which limited comparison, one trial [13,27,28] initiated follow-up after treatment started, and the other [29,30] reviewed patients following treatment completion. Participants in Brown et al. [29,30] were encouraged to maintain oral intake in addition to full delivery of EN support, this information was not reported in the other RCT [13,27,28]. Confounding factors to dysphagia such as treatment modalities, tumour location and cancer stage were not considered in these studies, which added further uncertainty to the effect of EN timing support on dysphagia. It is noteworthy to mention that the combined approach of oral intake and full EN delivery in Brown et al. [29,30] may have assisted more than half of the participants with maintaining swallowing function and returning to full diet.

No negative effects of prophylactic EN on swallowing outcomes were observed. However, dysphagia has been suggested as a possible prognostic factor for tube dependency at 12-months [29] and is consistent with Wopken et al. [22]. It is difficult to conclude whether it was EN timing or the pre-existing dysphagia that led to prolonged tube feeding, as pre-existing dysphagia is a clinical indicator for EN commencement in some institutions [29,30]. Moreover, a recent study [34] identified the T-stage extent and number of days nil by mouth (NBM) as significant risk factors for tube dependency at 12 months in patients with pPEG. Additionally, patients who had underwent intensity-modulated radiation therapy and had seen a speech pathologist during treatment had

shorter NBM time and less likely to be tube dependent [34]. This may suggest the importance of multidisciplinary management for reducing tube feeding duration and transitioning from EN to oral intake.

4.1. Strengths and limitation

A major strength of this systematic review is the inclusion of only RCTs and the use of reliable and robust methods, RoB2 and GRADE, to assess evidence. Previous systematic reviews and meta-analysis of this topic have included mostly non-randomised studies and have not used GRADE as part of their analysis [7,14,18,22]. McClelland et al. [14] and Wopken et al. [22] did not report any quality assessment, Shaw et al. [7] utilised the Cochrane risk-of-bias tool for quality assessment and Zhang et al. [18] used the Newcastle–Ottawa Scale for observational studies and the Cochrane Handbook for systematic reviews of interventions for RCTs. Furthermore, this review included three newly published manuscripts [28–30], which were not included in previous syntheses [7,14,18]. One of the new manuscripts [28] reported long term outcomes of the Silander et al. [13,27] RCT, and two others [29,30] reported a newly-conducted RCT.

Despite this new evidence, a definitive conclusion could not be reached due to small sample sizes, heterogeneity in the definitions and protocols for prophylactic and reactive EN approaches, variations in timepoints for outcome assessment and indirect dysphagia measures. The long-term swallowing outcomes at 24 months and 8 years reported in Silander et al. [27] and Axelsson et al. [28] may not be an accurate evaluation of the impact of pPEG due to potential confounding factors such as stroke, ageing and neurological disorders. Most of the included studies, as well as previous reviews on this topic, have failed to differentiate clearly between prophylactic tube placement and prophylactic tube feeding, which limits the ability to make comparisons. Furthermore, in the RCT by Silander et al. [13,27] and Axelsson et al. [28], most participants in the control group received rNGT ($n = 45/70$) or no EN ($n = 19/70$), compared to rPEG ($n = 6/70$). This limited comparison to Brown et al. [29,30], in which all received PEG.

5. Conclusion

In patients with HNC undergoing RT or CRT of curative-intent in definitive or adjuvant settings, Certainty of evidence regarding the timing of EN is low for short-term and moderate for long-term feeding duration, low for tube-related complications and very low for dysphagia. Large well-designed trials with consistent tube feeding protocols, direct dysphagia assessment tools and increased follow-up frequency are required to determine the optimal timing of EN for patients with HNC.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

Xiaodan Ye: Conceptualisation, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing Yuan-Chin Chang: Conceptualisation, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing Merran Findlay: Conceptualisation, Methodology, Writing – Review & Editing, Supervision Teresa Brown: Conceptualisation, Methodology, Writing –

Review & Editing, Supervision Judy Bauer: Conceptualisation, Methodology, Writing – Review & Editing, Supervision.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnesp.2021.05.017>.

References

- [1] Cancer-Council. Head and neck cancer Canberra. AIHW; 2020 [updated 2020 Jan 13. Available from: https://www.cancer.org.au/about-cancer/types-of-cancer/head-and-neck-cancer.html#jump_1.
- [2] Broccolo F, Ciccarese G, Rossi A, Anselmi L, Drago F, Toniolo A. Human papillomavirus (HPV) and Epstein-Barr virus (EBV) in keratinizing versus non-keratinizing squamous cell carcinoma of the oropharynx. *Infect Agents Canc* 2018;13(1).
- [3] McDermott JD, Bowles DW. Epidemiology of head and neck squamous cell carcinomas: impact on staging and prevention strategies. *Curr Treat Options Oncol* 2019;20(5):43.
- [4] Australian-Institute-of-Health-and-Welfare. Head and neck cancer in Australia. Canberra: AIHW; 2014.
- [5] Zackrisson B, Mercke C, Strander H, Wennerberg J, Cavallin-Staahl E. A systematic overview of radiation therapy effects in head and neck cancer. *Acta Oncol* 2003;42(5–6):443–61.
- [6] Gorenc M, Kozjek NR, Strojani P. Malnutrition and cachexia in patients with head and neck cancer treated with (chemo)radiotherapy. *Rep Practical Oncol Radiother* 2015;20(4):249–58.
- [7] Shaw S, Flowers H, O'Sullivan B, Hope A, Liu L, Martino R. The effect of prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement on swallowing and swallow-related outcomes in patients undergoing radiotherapy for head and neck cancer: a systematic review. *Dedicated to advancing the art and science of deglutology* 2015; p. 152–75. 2.
- [8] Nugent B, Lewis S, O'Sullivan JM. Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy. *Cochrane Database Syst Rev* 2013;(1): CD007904–. 2013.
- [9] Dwyer MK, Watts DD, Thurber SJ, Benoit SR, Fakhry MS. Percutaneous endoscopic gastrostomy: the preferred method of elective feeding tube placement in trauma patients. *J Trauma Inj Infect Crit Care* 2002;52(1):26–32.
- [10] Pearce C, Duncan H. Enteral feeding. Nasogastric, nasojunctional, percutaneous endoscopic gastrostomy, or jejunostomy: its indications and limitations. *Postgrad Med* 2002;78(918):198–204.
- [11] Tucker AT, Gourin CG, Ghegan MD, Porubsky ES, Martindale RG, Terns DJ. 'Push' versus 'pull' percutaneous endoscopic gastrostomy tube placement in patients with advanced head and neck cancer. *Laryngoscope* 2003;113(11): 1898–902.
- [12] Bradley TP, Brown TT, Paleri TV. Gastrostomy in head and neck cancer: current literature, controversies and research. *Curr Opin Otolaryngol Head Neck Surg* 2015;23(2):162–70.
- [13] Silander E, Nyman J, Bove M, Johansson L, Larsson S, Hammerlid E. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer — a randomized study. *Head Neck* 2012;34(1):1–9.
- [14] McClelland S, Andrews JZ, Chaudhry H, Teckie S, Goenka A. Prophylactic versus reactive gastrostomy tube placement in advanced head and neck cancer treated with definitive chemoradiotherapy: a systematic review. *Oral Oncol* 2018;87:77–81.
- [15] Anwender T, Bergé S, Appel T, von Lindern J-J, Martini M, Mommsen J, et al. Percutaneous endoscopic gastrostomy for long-term feeding of patients with oropharyngeal tumors. *Nutr Canc* 2004;50(1):40–5.
- [16] Piquet M-A, Ozsahin M, Larpin I, Zouhair A, Coti P, Monney M, et al. Early nutritional intervention in oropharyngeal cancer patients undergoing radiotherapy. *Support Care Canc* 2002;10(6):502–4.
- [17] Beer KT, Krause KB, Zuercher T, Stanga Z. Early percutaneous endoscopic gastrostomy insertion maintains nutritional state in patients with aerodigestive tract cancer. *Nutr Canc* 2005;52(1):29–34.
- [18] Zhang Z, Zhu Y, Ling Y, Zhang L, Wan H. Comparative effects of different enteral feeding methods in head and neck cancer patients receiving radiotherapy or chemoradiotherapy: a network meta-analysis. *Oncotargets Ther* 2016;9:2897–909.
- [19] Findlay M, Bauer J, Brown T. Head-and-Neck-Guideline-Steering-Committee. Summary of recommendations; 2014 [updated 2014 June 6. Available from: https://wiki.cancer.org.au/australia/COSA:Head_and_neck_cancer_nutrition_guidelines/Summary_of_recommendations.
- [20] Locher JL, Bonner JA, Carroll WR, Caudell JJ, Keith JN, Kilgore ML, et al. Prophylactic percutaneous endoscopic gastrostomy tube placement in treatment of head and neck cancer: a comprehensive review and call for evidence-based medicine. *J Parenter Enter Nutr* 2011;35(3):365–74.
- [21] Rogers SN, Thomson R, O'Toole P, Lowe D. Patients experience with long-term percutaneous endoscopic gastrostomy feeding following primary surgery for oral and oropharyngeal cancer. *Oral Oncol* 2007;43(5):499–507.
- [22] Wopken K, Bijl HP, Langendijk JA. Prognostic factors for tube feeding dependence after curative (chemo-) radiation in head and neck cancer: a systematic review of literature. *Radiother Oncol* 2018;126(1):56–67.
- [23] Krom H, Winter J, Kindermann A. Development, prevention, and treatment of feeding tube dependency. *Eur J Pediatr* 2017;176(6):683–8.
- [24] Talwar B, Findlay M. When is the optimal time for placing a gastrostomy in patients undergoing treatment for head and neck cancer? *Curr Opin Support Palliat Care* 2012;6(1):41–53.
- [25] Cancer-Council-Australia. Understanding head and neck cancers. 2019 [updated Sep 2019. Available from: <https://www.cancercouncil.com.au/wp-content/uploads/2020/04/Understanding-Head-and-Neck-Cancers-2019.pdf>.
- [26] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151(4):264–9.
- [27] Silander E, Jacobsson I, Bertéus-Forslund H, Hammerlid E. Energy intake and sources of nutritional support in patients with head and neck cancer—a randomised longitudinal study. *Eur J Clin Nutr* 2013;67(1):47.
- [28] Axelsson L, Silander E, Nyman J, Bove M, Johansson L, Hammerlid E. Effect of prophylactic percutaneous endoscopic gastrostomy tube on swallowing in advanced head and neck cancer: a randomized controlled study. *Head Neck* 2017;39(5):908–15.
- [29] Brown T, Banks M, Hughes B, Lin C, Kenny LM, Bauer J. Randomised controlled trial of early prophylactic feeding vs standard care in patients with head and neck cancer. *Br J Canc* 2017a;117(1).
- [30] Brown T, Banks M, Hughes BGM, Lin C, Kenny LM, Bauer JD. Impact of early prophylactic feeding on long term tube dependency outcomes in patients with head and neck cancer. *Oral Oncol* 2017b;72:17–25.
- [31] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366.
- [32] GRADEpro-GDT. GRADEpro guideline development tool [software]; McMaster university (developed by evidence prime, inc.). 2020 [Available from: <https://gradepr.org/>].
- [33] McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods* 2021;12(1):55–61.
- [34] Fraser A, Odelli C, Britton B, Kumar M, Day F, Tieu MT, et al. Gastrostomy dependency trends over 15 years of patients at a large tertiary referral center following the insertion of a prophylactic gastrostomy for chemo-radiation for mucosal head and neck cancer. *Asia Pac J Clin Oncol* 2020;16(5):e198–206.