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Effectivity of Prophylactic Enteral Nutrition on Weight Loss in Head and neck Cancer Patients Undergoing Radiotherapy and/or Chemotherapy: A Case Study with Evidence-Based Approaches

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ABSTRACT

Background: Globocan data shows that head and neck cancer in Indonesia ranks as the 5th leading cause of cancer in 2020 with 19,943 new cases per year and 13,399 deaths. Chemotherapy along with radiation therapy is the main management for advanced nasopharyngeal cancer to control local recurrence and prolong survival. However, it can cause side effects such as mucositis, dysphagia, fatigue, and anorexia, which cause weight loss and exacerbate malnutrition. Studies examining the effectiveness of prophylactic enteral nutrition to prevent weight loss in a population of head and neck cancer patients undergoing radiotherapy and/or chemotherapy have not been widely conducted and the results are still controversial.

Objective: To determine the effectiveness of prophylactic enteral nutrition in preventing weight loss in head and neck cancer patients undergoing radiotherapy and/or chemotherapy.

Method: This study used literature search on PubMed, Cochrane Library, and Scopus databases to retrieve SR-MA and RCT articles that fit the clinical question of this case study.

Result: There are three articles that are relevant to the clinical questions and eligibility criteria that have been established, consisting of one Meta-Analysis (MA) article and two Systematic Review (SR) articles. There was one SR that only analyzed RCTs, while one MA and other SRs included both prospective and retrospective cohorts in their analysis. Two SRs reported no significant difference in weight loss between the prophylactic enteral nutrition (EN) intervention group and the reactive EN control group. While one MA found a significant difference in weight loss between the two groups studied. However, high heterogeneity was obtained in the data.

Conclusion: The evidence that supports the effectiveness of prophylactic enteral nutrition (EN) in preventing weight loss in head and neck cancer patients has not yet been obtained with certainty, but patients who receiving prophylactic EN were less likely to experience short term critical weight loss. Various studies carried out on this topic report varying results with low research quality. Therefore, further research into better design is needed to find conclusive results.

Keywords: chemotherapy, chemoradiotherapy, enteral nutrition, head

and neck cancer, radiotherapy, tube feeding, weight loss.

INTRODUCTION

Head and neck cancer (HNC) is a cancer that involves the oral cavity, pharynx, hypopharynx, larynx, nasal cavity and salivary glands.[1] According to 2020 Globocan data, nasopharyngeal cancer in Indonesia is the 5th most common cause of cancer with 19,943 new cases and 13,399 deaths annually.[2] Chemotherapy along with radiation therapy is the main treatment for advanced HNC. Radiotherapy or chemoradiotherapy is the best treatment in control local recurrence and prolong survival.[3-5] The patient undergoing chemotherapy and Intensity-Modulated Radiation Therapy (IMRT) for HNC experienced several side effects. IMRT precisely targets tumor cells with high doses, but also damages healthy tissue, causing complications like oral mucositis (radiotherapy induced oral mucositis, ROM), xerostomia (dry mouth), and taste disturbances. Acute side effects, such as oral mucositis and dry mouth, begin during treatment and last for weeks, while chronic effects, like trismus and dental caries, can emerge much later.[6,7] Xerostomia, persistent with radiation doses above 40 Gy, significantly impacts oral health and leads to other complications. Severe ROM, experienced by 34-66% of patients, causes significant pain, ulceration, necrosis, and malnutrition, often linked to weight loss and poor nutritional status. Continuous low-dose chemotherapy also increases the risk of mucositis, requiring careful management of treatment and side effects.[8,9] Malnutrition in cancer patients is associated with longer hospital stay, decreased quality of life, and negative impact on effectiveness of anticancer therapy, thus worsening the prognosis. Early nutritional support is essential to mitigate these effects.[10,11]

According to ESPEN guidelines, whether oral nutrition is insufficient even with the use of oral nutritional supplements (ONS), or enteral nutrition should be considered. For head and neck cancer patients undergoing radiation therapy, enteral nutrition can be provided through a nasogastric tube (NGT) or percutaneous endoscopic gastrostomy (PEG).[12] Studies conducted by Lee et al and Tyldesley et al stated that PEG placement before radiotherapy was associated with less weight loss and shorter hospital stay compared to PEG placement after radiotherapy.[13,14] Studies conducted by McClelland et al stated that prophylactic enteral nutrition with PEG was associated with decreased malnutrition rates and improved quality of life in head-neck cancer patients.[15]

As weight loss increases the risk of malnutrition and it is linked to worse outcomes in head and neck cancer patients, a literature search aiming for high quality evidence is required to answer clinical questions about the effect of prophylactic enteral nutrition on weight loss in head and neck cancer patients receiving radiotherapy and/or chemotherapy.

CLINICAL QUESTION

"Does prophylactic feeding tube supplementation effective to improve clinical outcome in head and neck cancer patients receiving radiotherapy or chemoradiotherapy?"

Participants (P) : adult head and neck cancer patients receiving radiotherapy or chemoradiotherapy

Intervention (I) : prophylactic feeding tube (NGT or PEG) placement

Control (C) : feeding tube placement as indicated

Outcome (O) : weight loss

CASE REPORT

A 54-year-old female patient diagnosed with Squamous Cell Carcinoma of Nasopharynx was referred to Nutrition outpatient clinic Dr. Cipto Mangunkusumo General Hospital from Oncology-Radiation out clinic patient as she was screened at risk for malnutrition with MST score of 2. Patients planned to receive EBRT/IMRT

(External Beam Radiation Therapy/Intensity Modulated Radiation Therapy) with a dose of 70/60/54 Gy in 33 fractions and chemosensitizer therapy with a weekly regimen of cisplatin.

On the first visit to the nutrition clinic, the patient had already undergone the first of 33 fractions of radiation, while chemotherapy was still pending. The patient complained of pain in the right shoulder, ringing in the right ear, and hearing loss. There were no complaints about nausea or vomiting. Her appetite was good. Bowel and urinary functions were normal. During the second visit to the nutrition clinic, the patient had undergone the seventh of 33 fractions of radiation and one session of chemotherapy. The patient complained of nausea accompanied by vomiting three times a day, with yellow fluid mixed with food, and has already been prescribed an ondansetron 8 mg three times a day and omeprazole 1 capsule twice a day. The patient also reported thick saliva, dry mouth, and pain when swallowing. The patient denied having mouth sores. The patient preferred soft, brothy, and liquid foods. The patient experienced a weight loss of 1.4 kg (2%) in the past 10 days.

Radiation-induced oral mucositis (ROM) affects nearly all nasopharyngeal cancer patients, with 34–66% experiencing grade 3 ROM. In mild ROM (≤ grade 2), 38% of patients have difficulty with food intake, while severe ROM results in intense mouth pain, ulceration, necrosis, and malnutrition due to difficulty consuming food. Li et al. reported that weight loss of ≥5% is a risk factor for severe ROM. This is because malnutrition can impair mucosal regeneration due to reduced cellular migration caused by poor nutritional status. Early nutritional support as feeding tube placement is necessary to prevent the development of severe ROM, to prevent malnutrition related to ROM and improve clinical outcomes. Stronger evidence is needed.

METHODS

Searching strategy

Literature search was conducted on three databases PubMed, Cochrane Library, and Scopus by combining MeSH Terms and title/abstract of each PICO component and study design and using the Boolean operator "OR" to increase sensitivity and "AND" to increase specificity (Table 1). The keywords used were "Neoplasm, head and neck", "Cancer of head and neck", "radiotherapy", chemotherapy", chemoradiotherapy", "radiochemotherapy", "prophy*", "enteral nutrition", "enteral feeding", "nasogastric", "percutaneous endoscopic gastrostomy", "NGT", "PEG", "weight loss", "malnutrition", "malnourished", "systematic review", "meta-analysis", "randomized controlled trial". The retrieved articles then screened for duplication and asessed for the PICO's similarity with this case study. Articles that fit the clinical question of this case study were included for critical appraisal using tools from CEBM (Centre for Evidence Based Medicine).

Eligibility Criteria

Inclusion criteria: 1) study participants were adult head and neck cancer patients planned to or undergoing radiotherapy or chemoradiotherapy; 2) intervention was prophylactic feeding tube (NGT or PEG) placement versus feeding tube placement as indicated; 3) outcomes are weight loss with or without other outcomes; 4) research with a systematic review/meta-analysis (SR-MA) design of randomized controlled trials (RCT), as well as research with a RCT design.

Exclusion criteria: 1) studies involving subjects who had received enteral nutrition prior to radiotherapy and/or chemotherapy due to poor tolerance of oral intake.; 2) articles published in languages other than English and Indonesia language; 3) ongoing study.

Table 1. Literature search strategy

Database	Search Strategy		Hits
PubMed	(((((((Neoplasms, Head[Title/Abstract] AND Neck[Title/Abstract]) OR (Neoplasms, Head and Neck[MeSH Terms])) OR (Cancer of Head[Title/Abstract] AND Neck[Title/Abstract])) OR (Cancer of Head and Neck[MeSH Terms])) AND ((((((((Radiotherapy[Title/Abstract]) OR (Radiotherapy[MeSH Terms])) OR (Chemotherapy[Title/Abstract])) OR (Chemotherapy[MeSH Terms])) OR (Chemoradiotherapy[Title/Abstract])) OR (Chemoradiotherapy[MeSH Terms])) OR (radiochemotherapy[Title/Abstract])) OR (radiochemotherapy[MeSH Terms]))) AND ((((((((((((prophy*[Title/Abstract]) OR (prophy*[MeSH Terms])) OR (enteral nutrition[Title/Abstract])) OR (enteral nutrition[MeSH Terms])) OR (enteral feeding[Title/Abstract])) OR (enteral feeding[MeSH Terms])) OR (nasogastric[Title/Abstract])) OR (nasogastric[MeSH Terms])) OR (percutaneous endoscopic gastrostomy[Title/Abstract])) OR (percutaneous endoscopic gastrostomy[MeSH Terms])) OR (NGT[Title/Abstract])) OR (NGT[MeSH Terms])) OR (PEG[Title/Abstract])) OR (PEG[MeSH Terms]))) AND ((((((((meta analysis[Title/Abstract]) OR (meta analysis[Title/Abstract])) OR (systematic review[Title/Abstract])) OR (systematic review[MeSH Terms])) OR (randomized controlled trial[Title/Abstract])) OR (randomized controlled trial[MeSH Terms])) OR (network meta-analysis[Title/Abstract])) OR (network meta-analysis[MeSH Terms]))) AND ((((((((weight loss[Title/Abstract]) OR (weight loss[MeSH Terms])) OR (malnutrition[Title/Abstract])) OR (malnutrition[MeSH Terms])) OR (malnourished[Title/Abstract])) OR (malnourished[MeSH Terms])) OR (nutrition status[Title/Abstract])) OR (nutrition status[MeSH Terms]))		18
Cochrane Library	ID	Search Hits	25
	#1	(neoplasm AND head AND neck): ti,ab,kw OR (cancer AND head AND neck): ti,ab,kw	
	#2	(radiotherapy):ti,ab,kw OR (chemotherapy): ti,ab,kw OR (radiochemotherapy): ti,ab,kw AND (chemoradiotherapy):ti,ab,kw	
	#3	(prophy*):ti,ab,kw AND (enteral AND nutrition):ti,ab,kw OR (enteral AND feeding):ti,ab,kw OR (percutaneous AND endoscopic AND gastrostomy):ti,ab,kw OR (nasogastric):ti,ab,kw	
	#4	(weight AND loss):ti,ab,kw OR (malnutrition):ti,ab,kw OR (malnourished):ti,ab,kw OR (nutrition status):ti,ab,kw	
	#5	#1 AND #2 AND #3 AND #4	
Scopus	(TITLE-ABS-KEY (neoplasm AND head AND neck) OR TITLE-ABS-KEY (cancer AND head AND neck) AND TITLE-ABS-KEY (radiotherapy) OR TITLE-ABS-KEY (chemotherapy) OR TITLE-ABS-KEY (radiochemotherapy) OR TITLE-ABS-KEY (chemoradiotherapy) AND TITLE-ABS-KEY (prophy* AND enteral AND feeding) OR TITLE-ABS-KEY (prophy* AND enteral AND nutrition) OR TITLE-ABS-KEY (prophy* AND nasogastric) OR TITLE-ABS-KEY (prophy* AND percutaneous AND endoscopic AND gastrostomy) AND TITLE-ABS-KEY (weight AND loss) OR TITLE-ABS-KEY (malnutrition) OR TITLE-ABS-KEY (malnourished) OR TITLE-ABS-KEY (nutrition AND status) AND TITLE-ABS-KEY (systematic AND review) OR TITLE-ABS-KEY (meta AND analysis) OR TITLE-ABS-KEY (randomized AND controlled AND trial))		19

RESULT

The flow diagram of the literature search is illustrated in Fig. 1. Sixty-two articles were initially identified from the 3 databases. After removing duplicate articles, 45 articles were screened for eligibility based on abstract and full text. There were 3 RCT articles already included in a SR-MA article thus they were excluded. Finally, 3 full text articles of 2 SR-MA and 1 RCT article were selected for critical appraisal. Characteristics of selected articles in presented in Table 2. The selected articles were critically appraised to review the validity, importance and applicability. A summary of critical appraisal results of each article is presented in Table 3 and 4.

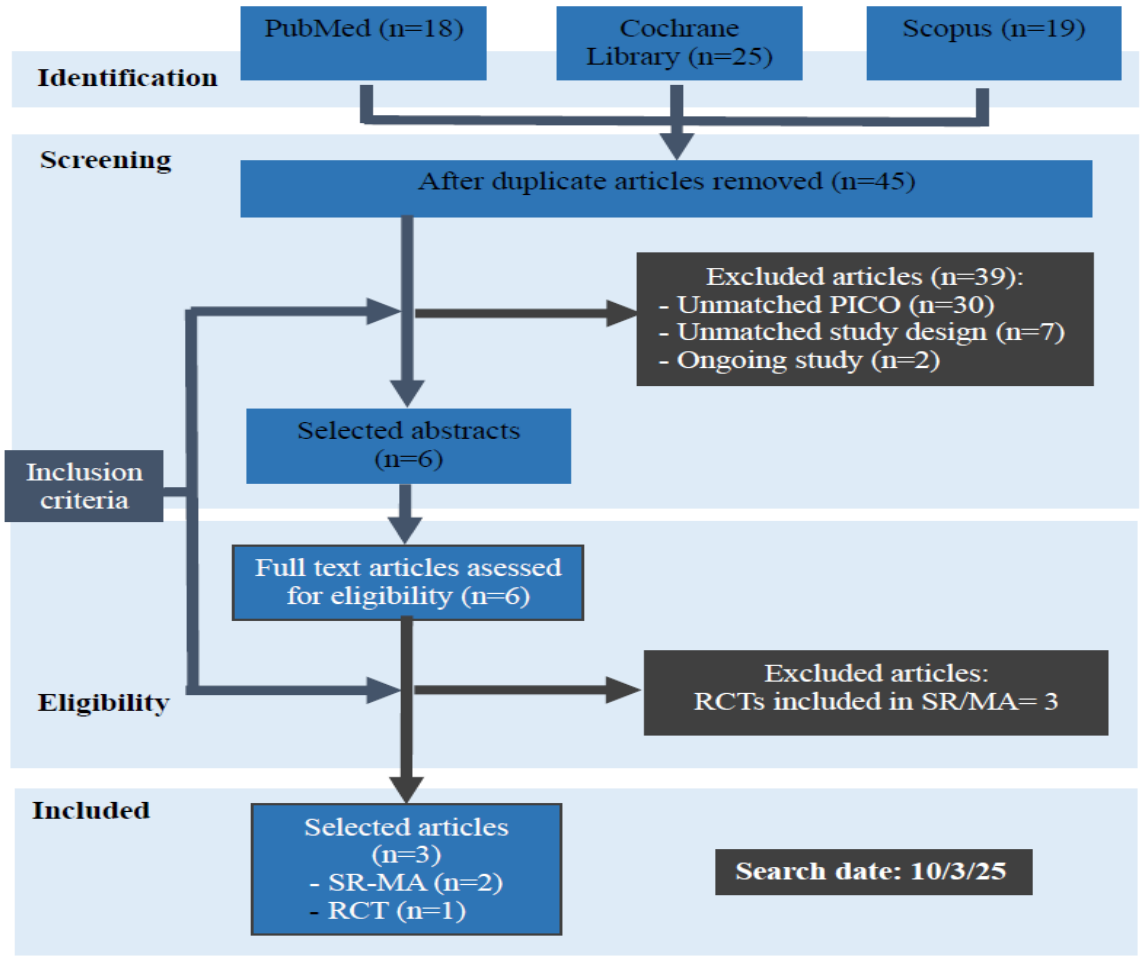

Figure 1. The flow diagram of literature search

Table 2. Characteristics of selected articles

Article	Study Design	Population	Intervention	Outcome
Mellors K et al. (2021)[16]	Systematic review of randomized controlled trial	3 RCTs (N=298), head and neck cancer patients undergoing radiotherapy, chemotherapy, or combination who receiving pPEG or rEN (PEG or NGT)	146 subjects of 3 RCTs received prophylactic PEG, while the rest subjects received PEG when considered necessary	Weight change, nutritional status, BMI, treatment interruptions, QoL, disease-free and overall survival
McClelland S et al. (2018)[15]	Systematic review of cohort studies	7 cohort studies (N=676), head and neck cancer receiving chemotherapy	498 subjects received prophylactic PEG placement when the rest subjects received PEG when considered necessary	Weight change, 6-month QoL, toxicity, PEG dependence, survival, disease control.
Zhang et al. (2016)[17]	Systematic review and meta-analysis of randomized controlled trials and cohort studies	11 cohort studies and 2 RCTs (N=1531), head and neck cancer patients receiving radiotherapy or radiochemotherapy	730 subjects received prophylactic PEG or NGt placement when the rest subjects received PEG or NGT when considered necessary or oral feeding	Weight change, interruption of treatment, tube-related complications, hospital admission.

Table 3. Summary of critical appraisal result of a SR-MA articles

	Study Design	**Question**	**Find**	**Appraise**	**Inclusion**	**Total Up**	**Heterogeneity**	**Result**	**Applicability**	**Level of Evidence**
Mellors K et al. (2021)[16]	Systematic review of randomized controlled trial	+	+	+	+	+	Unclear	A	+	Level 1a
Mc-Clelland S et al. (2018)[15]	Systematic review of cohort studies	+	+	Unclear	Unclear	Unclear	Unclear	B	+	Level 1a
Zhang et al. (2016)[17]	Systematic Review & Meta Analysis of randomized controlled trial	+	+	+	Unclear	+	+	C	+	Level 1a

A: No significant difference in weight loss between prophylactic PEG and reactive EN groups at 3-months post treatment (10.8% vs 10.9%, p=0.93), at 6-months post treatment (11.2% vs 12.4%, p=0.08), at 12-months post treatment (11.1% vs 11.7%, p=0.52), and at 24-months post treatment (8.9% vs 6.6%, p=0.33). However, the prophylactic PEG group lost significantly less weight compared to reactive EN group (11,4% vs 13.6%, p=0.03).

B: No significant difference in weight loss between prophylactic PEG and reactive EN (-8.8 kg [11.2%] vs -9.6 kg [12.4%], p = 0.08).

C: The results of the study comparing prophylactic PEG with reactive PEG on weight loss, obtained standardized mean difference (SMD) = 1.38, 95% CI: 0.91-1.84, I2 = 79%. Meanwhile, the results of a study comparing prophylactic PEG and without PEG on weight loss, obtained SMD = 0.45, 95% CI: 0.14-0.76, I2 = 86.9%.

DISCUSSION

We collected two systematic reviews and one meta-analysis to answer clinical questions regarding the effectiveness of prophylactic enteral nutrition in preventing weight loss in head and neck cancer patients undergoing radiotherapy and/or chemoradiotherapy. Our critical review found that the three articles still had shortcomings in terms of validity. We were also unable to find conclusive answers to the clinical questions we asked due to differences in results between the three articles we collected. Although in the conclusion, all three articles agree in supporting the use of prophylactic PEG as an early enteral nutrition intervention in head and neck cancer patients to prevent significant weight loss.

The study by Mellors, et al reported no significant difference in weight loss between the intervention and control groups (-10.8 kg ± 5.6 vs. -10.9 kg ± 6.6, p=0.326) when observed over a period of 3-months. The same results were also obtained at 6-months of observation (-8.8 kg [11.2%] vs. control: -9.6 kg [12.4%], p=0.08). An analysis was carried out only on patients who experienced weight loss, it was found that the group that received prophylactic PEG experienced less weight loss than controls with a significant difference (11.4% versus 13.6%, p = 0.03). However, this study also acknowledges the weaknesses in terms of the fairly high risk of bias of RCTs and the heterogeneity of data due to population differences, differences in prophylactic and reactive PEG procedures, and differences in anti-cancer therapy regimens which reduce the applicability of the results of this study.[16] Although studies showed no statistically significant difference in short- and long-term weight changes between patients receiving prophylactic PEG (pPEG) and those using reactive enteral nutrition (rEN), more patients with pPEG were less likely to experience critical weight loss (>10%) within six months. This is clinically important because weight loss itself is an independent predictor of six-month survival.[18] Furthermore, weight loss tended to stop once patients met their energy needs, and those who adhered better to the prescribed enteral feeding regimen (consuming at least 75% of their formula) lost significantly less weight than non-adherent patients. This highlights the importance of patient compliance and close clinical monitoring throughout treatment and follow-up. To support better adherence, strategies such as nutrition education and behavior change interventions could help maintain nutritional status during therapy.[19,20]

McClelland, et al reported similar result in their study. They stated that there was no significant difference in weight loss between the intervention (pPEG) and control (rPEG) groups (8.8 kg vs 9.6 kg with p = 0.08). Patients with greater weight loss (weight loss >10%) were found more in the control group.[15] This result aligns with a prospective cohort study by Brown et al. The use of prophylactic PEG (pPEG) was linked to better nutritional outcomes. The study involved 130 high-nutritional-risk patients who either received pPEG according to the treatment protocol or did not receive it before starting chemoradiation. Weight loss was influenced by factors such as age, tumor location, patient group, and the treating physicians. On average, patients who did not receive a PEG lost 2% more body weight compared to those in the pPEG group.[21] However, as explained in the critical review above, this study does not explain the risk of bias in the studies analysed and included studies with a cohort design in its analysis.[15] In addition, there is considerable variation across studies regarding the percentage of patients managed with a rPEG approach who ultimately require PEG placement. For instance, Chen et al[22] reported that 32% of patients needed PEG, whereas Silander et al[23] found a much higher rate of 72.9% in their cohort. The data suggest several factors that can help identify patients who are most likely to need enteral nutrition during treatment, such as older age, weight

loss at diagnosis, and the amount of radiation delivered to the pharyngeal constrictor muscles. Ideally, all HNC patients being considered for pPEG should undergo a modified barium swallow (MBS) or a formal swallowing assessment before a decision is made. These evaluations combined with details like tumor site, treatment area, patient age, and initial weight loss could help determine which patients are at the highest risk of malnutrition. For those high-risk patients, pPEG is recommended. If a rPEG strategy is chosen instead, it's crucial to closely monitor the patient's condition and provide comprehensive support, including detailed nutritional counseling and effective management of mucositis and pain, to reduce the risk of weight loss and dehydration.[15]

Meanwhile, a study conducted by Zhang, et al obtained significant results for the difference in weight loss between groups receiving pPEG with rPEG control (HR = 1.38, 95% CI: 0.91-1.84, I2 = 79%), and with control without pPEG (PEG, NGT or reactive oral nutrition) (HR = 0.45, 95% CI: 0.14-0.76, I2 = 86.9%). This study also reported that pPEG and NGT were preferable to rPEG on weight loss management. Although NGT showed higher surface under the cumulative ranking curve (SUCRA) probabilities than pPEG in terms of body weight change, this advantage may be due to patients with NGT generally having better performance status and overall clinical condition. Early nutritional intervention was associated with improved nutritional status, better tolerance to treatment, and reduced hospital admissions. However, this study also acknowledged that the reliability of their findings was quite weak because this study also included cohort studies in their analysis. In addition, this study did not explain the heterogeneity of the data they found.[17]

The studies that have been described above show that until now there has been no research on the effectiveness of prophylactic enteral nutrition in preventing weight loss in head and neck cancer patients undergoing radiotherapy and/or chemotherapy that has good research quality with conclusive results. However, there is a tendency for greater benefits from providing prophylactic enteral nutrition, especially PEG, compared to no prophylactic enteral nutrition or reactive enteral nutrition. A successful prophylactic enteral nutrition approach requires a multidisciplinary team, including surgeons, medical and radiation oncologists, speech-language pathologists, clinical nutritionists, dietitians, and gastroenterologists, to ensure coordinated care and optimal outcomes.

Although there is no conclusive evidence, prophylactic enteral nutrition interventions can still be carried out with close monitoring of the development of the patient's nutritional status. Apart from the controversial results regarding the effectiveness of prophylactic enteral nutrition in head and neck cancer patients who will undergo therapy, in the clinical scenario, a 54-years old woman with head and neck cancer who receiving chemoradiotherapy and has experienced a weight loss of 1.4 kg (2%) in 10 days, it is necessary to consider providing prophylactic enteral nutrition to prevent further weight loss.

CONCLUSION

The effectiveness of prophylactic enteral nutrition to prevent weight loss in head and neck cancer patients undergoing radiotherapy and/or chemoradiotherapy has not been fully understood due to inconsistent research results and the limited number of good quality studies on this topic. Although studies did not find statistically significant differences in short- or long-term weight changes between patients receiving prophylactic EN and those managed with reactive EN, patients with pPEG were less likely to experience significant weight loss (greater than 10%) within six months. This is clinically relevant, as weight loss is an independent predictor of six-month overall survival. These findings underscore the

importance of patient adherence and consistent clinical monitoring throughout the course of treatment and follow-up. To support adherence, implementing strategies such as nutrition education and behavior change interventions may help maintain optimal nutritional status during therapy. In addition, more research is needed in the future, especially well-conducted RCTs followed by systematic reviews and meta-analyses to reveal gaps in knowledge regarding this topic.

Declaration by Authors

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