



The Effects of Early Nutritional Intervention on Oral Mucositis and Nutritional Status of Patients With Head and Neck Cancer Treated With Radiotherapy

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Radiation-induced oral mucositis (RIOM) is a common side effect after radiotherapy (RT) in head and neck cancer (HNC) patients. RIOM patients with severe pain have difficulty in eating, which increases the incidence of malnutrition and affects patients' quality of life and the process of RT. The mechanism of RIOM is not fully understood, and inflammatory response and oxidative stress appear to be important for RIOM occurrence and development. The nutritional status of patients is very important for their RT tolerance and recovery. Malnutrition, which can lead to anemia, low protein, decreased immunity and other problems, is an important clinical factor affecting tumor progression and treatment. Recent studies have shown that early nutritional intervention can ameliorate oral mucositis and nutritional status of patients with HNC. However, in clinical practice, early nutritional intervention for patients with HNC is not a conventional intervention strategy. Therefore, this review summarized the possible pathogenesis of RIOM, commonly used assessment tools for malnutrition in patients, and recent studies on the effects of early nutritional interventions on RIOM and nutritional status of patients with HNC. We hope to provide the basis and reference for the clinical application of early nutritional intervention models.

Keywords: early nutritional intervention, head and neck cancer, radiotherapy, oral mucositis, malnutrition

Abbreviations: ADA, American Dietitian Association; BMI, Body Mass Index; ESPEN, European Society for Parenteral Nutrition; IL, interleukin; KGF, keratinocyte growth factor; LLLT, low-level laser therapy; MASCC/ISOO, the Multinational Association of Support Care in Cancer/International Society of Oral Oncology; MMPs, matrix metalloproteinases; MNA, mini nutrition assessment; MUST, malnutrition universal screening tool; NF- κ B, nuclear factor-kappaB; NRS2002, nutritional risk screening 2002; PBMT, photobiomodulation therapy; PEG, percutaneous endoscopic gastrostomy; PG-SGA, patient-generated subjective globe assessment; PPAR, peroxisome proliferator-activated receptor; PT, photodynamic therapy; RIOM, radiation-induced oral mucositis; ROS, reactive oxygen species; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; TGF- β , transforming growth factor; TNF- α , tumor necrosis factor alpha.

INTRODUCTION

Head and neck cancer (HNC) is the sixth most common cancer worldwide with more than half a million new cases diagnosed each year (1, 2). Because of the limitations imposed by the complicated anatomical structure of the head and neck to the operation, radiotherapy (RT) has become the main treatment method for HNC. However, damage to the normal tissue surrounding the tumor is inevitable. The most common manifestations of injury caused by RT are mucositis, dysphagia, pharyngeal pain, taste disorders, mouth dryness, nausea, vomiting, and anorexia, which may adversely affect the nutritional status of patients and lead to a decline in their quality of life (3–6).

Radiation-induced oral mucositis (RIOM) is a common side effect of RT for HNC. Studies have shown that patients with HNC have oral mucositis at various degrees, when the radiation dose reaches a certain level, and the incidence of \geq Grade 3 mucositis is as high as 56% (7, 8). RIOM, which usually starts at around the 5th to 10th RT fraction, occurs in $> 80\%$ of patients during RT. Hyperemia, erythema, and erosion may occur in patients' mucosa until severe ulcers and fibrosis appear (9). Severe pain makes it difficult for patients to eat and leads to malnutrition, which affects patients' quality of life and the course of RT (10, 11).

Malnutrition, which is caused by failure of food intake to provide the required energy, is an important clinical factor in the progression and treatment of cancer (12). RIOM is one of the key barriers to food intake. Most HNC patients experience weight loss after RT, and many suffer from moderate to severe malnutrition, which affects patients' quality of life and treatment process (13, 14). Weight loss in patients leads to changes in body shape, decreases immobilization of head and neck masks, and affects RT accuracy. Malnutrition can also lead to anemia, low protein, decreased immunity, and increased complications during RT.

Nutritional intervention is important for maintaining the nutritional status of patients with HNC. International guidelines recommend strengthening nutritional consultation and oral nutritional supplement as nutritional interventions for patients with HNC undergoing chemoradiotherapy (15, 16). Nutritional interventions that emphasize protein targets during RT may reduce severity of oral mucositis. Studies have shown that oral mucositis is less severe when patients with HNC achieve the corresponding protein and calorie intake targets during RT (17–19). However, in clinical practice, nutritional intervention usually begins when patients develop oral mucositis or severe gastrointestinal reactions that result in restricted feeding. The effect is limited, and it is difficult to effectively improve the nutritional status of patients. Therefore, early nutritional intervention may become an important treatment to prevent malnutrition. However, currently, early nutritional intervention for patients with HNC is not a conventional nutritional intervention strategy.

The purpose of this review was to analyze the effects of nutritional intervention on radiation-induced oral mucositis and malnutrition in patients in different periods, hence to

provide a basis and reference for the application of early nutritional intervention strategies in clinical practice. Therefore, we summarized and compared recent literature on the effects of traditional nutritional intervention and early nutritional intervention on the therapeutic outcome, oral mucosal complications, quality of life, and nutritional status of patients with HNC.

ORAL MUCOSITIS AND MALNUTRITION IN HNC PATIENTS WITH RT

Radiation-Induced Oral Mucositis

RIOM is one of the most important toxic reactions of normal tissue during RT for in HNC patients (8, 20). RIOM is classified into five grades according to Radiation Therapy Oncology Group standards (21): No changes were observed in Grade 0 mucositis. Grade 1 includes mucositis that causes mild pain or congestion that does not require analgesics. Grade 2 includes the development of patchy mucositis, the requirement for analgesics, or the production of serosanguineous discharge. Grade 3 includes the development of confluent mucositis or severe pain requiring narcotic analgesics, and Grade 4 involves the development of ulcer, necrosis, and bleeding from the area. Severe RIOM can cause severe pain, especially ulcers near the pharynx, which can cause severe pain when swallowed and loss of appetite. In addition, injury to the parotid gland and taste buds leads to decreased saliva and loss of taste, which also seriously affects the patient's appetite. When fibrosis occurs, the patient has difficulty opening his or her mouth, which can also affect food intake.

The development of RIOM is divided into five stages comprising initiation, signaling, amplification, ulceration, and healing. At the initial stage of injury, radiation deposits energy on biological macromolecules including protein molecules. Furthermore, the epithelium, blood vessels, and mesenchymal cells of the mucosa at the site of injury release reactive oxygen species (ROS) causing damage to DNA. Signal is transduced through matrix metalloproteinases (MMPs), nuclear factor kappa-B (NF- κ B), and ceramide pathways in macrophages. The signal amplification stage is mediated by pro-inflammatory cytokines including tumor necrosis factor alpha (TNF- α), interleukin 1 β (IL-1 β), and IL-6. Subsequently, mucosa desquamation of the epithelium occurs, and the basement membrane is damaged. The oral mucosa loses its protective barrier and eventually ulcerates. At the beginning of the healing phase, basal epithelial cells migrate, proliferate, and differentiate. The ulcer eventually heals. Changes in late stage ulcer are associated with a variety of factors, which may lead to secondary gram-negative bacterial infection. Infection may lead to blocked blood flow and ischemic necrosis, which cause more severe inflammatory changes that eventually heal in the form of fibrosis (20, 22, 23). Patients eat less because of severe oral pain, thereby becoming malnourished. In turn, malnutrition affects the severity and healing time of mucositis and ulcers. In addition, although RT combined with chemotherapy increases local tumor

control, it also increases the incidence of ulcerative mucositis and results in interruption of RT (24).

A number of risk factors have been associated with the development of RIOM. These mainly include combined chemotherapy, oral hygiene, low nutrition, early non-use of antibiotics, and smoking (25). Dose is the most important factor affecting RIOM and the dose of oral mucosa is not recommended to exceed 45Gy. With the accumulation of dose, severe RIOM occurred more frequently in weeks 5 and 6 of RT (26). Hyperfractionation is associated with more severe acute oral toxicities, primarily mucositis. One animal experiment showed that at day 10 after RT, the oral size % of mice was 2, 5, 27, and 31 percent for 15, 18, 20, and 25 Gy RT (27). RIOM membrane inflammation and ulcer play a very important role in tissue injury caused by IL-1, TNF- α , and other inflammatory cytokines released from epithelial cells, blood vessels, and connective tissue; these can increase the wall permeability of capillaries and the numbers of inflammatory cells, such as myeloperoxidase-positive leukocytes and macrophages and neutrophil infiltration (28). Production of ROS is a key link in the aggravation of inflammatory injury. Sonis et al. (29, 30) showed that signal amplification is the core link in the

development of RIOM into ulcer. Amplification of ROS and inflammatory cytokines occurs mainly through the following three steps: (1) activating the NF- κ B pro-inflammatory pathway, stimulating target gene expression, and producing a large number of inflammatory cytokines, such as TNF- α , IL-1, and IL-6, which activate the ceramide pathway, thereby producing large amounts of sphingomyelinase and ceramide synthase and eventually causing more tissue damage and cell apoptosis; (2) fibronectin breakdown, which stimulates macrophages leading to activation of MMPs; (3) impaired mitochondria produce more ROS, which activates the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome pathway. NLRP3 activates caspase-1, which produces IL-1 β and leads to apoptosis (31). In addition, the loss of a protective barrier in the basement membrane at the ulcer site increases the likelihood that gram-negative and yeast bacteria will develop secondary infections, which perpetuates inflammation and complicates existing inflammation (Figure 1).

Good oral hygiene can significantly reduce the risk of RIOM and is one of the most effective prevention methods, with only a few alternative effective treatments. Currently, symptomatic treatment is mostly adopted in clinical practice mainly

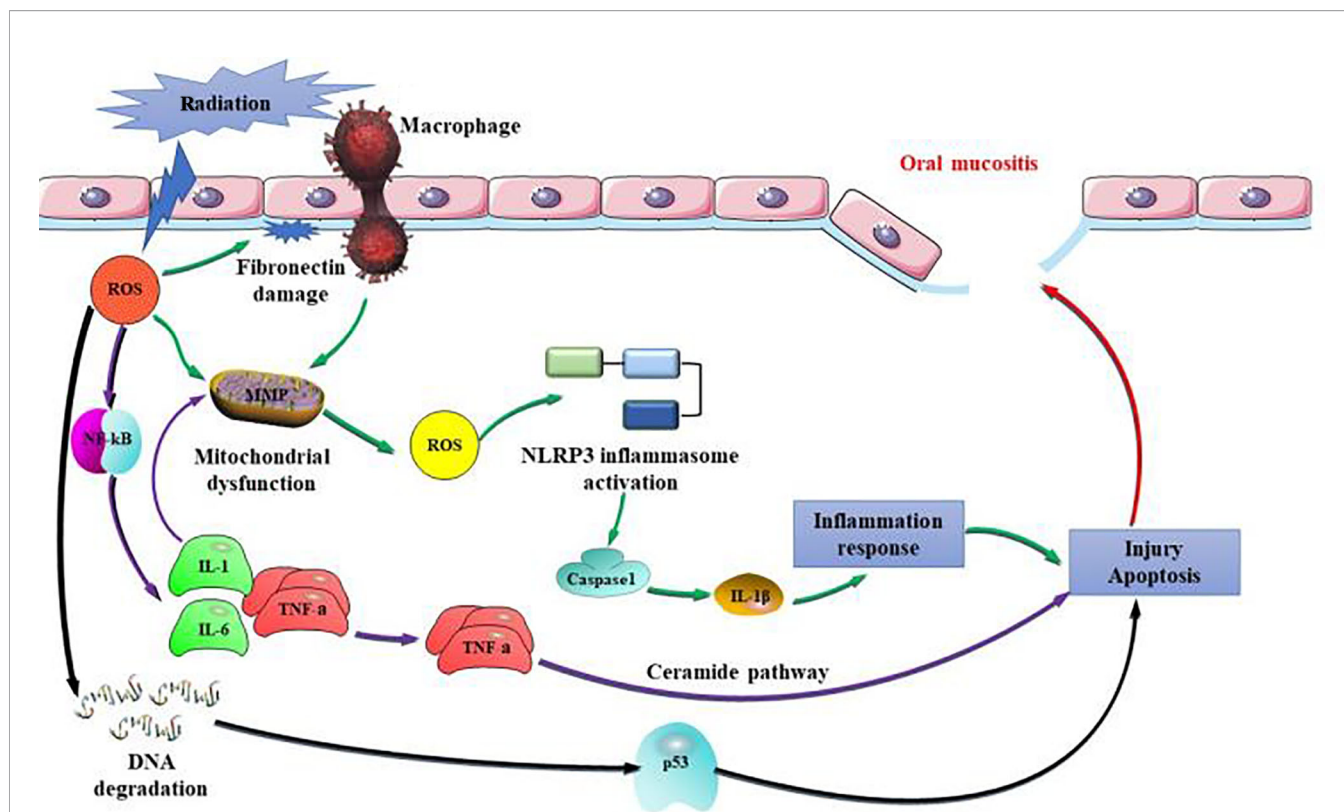


FIGURE 1 | Pathogenic mechanisms of radiation-induced oral mucositis (RIOM). Amplification of reactive oxygen species (ROS) and inflammatory cytokines occurs mainly through the following three steps: (1) activating the nuclear factor kappa-B (NF- κ B) pro-inflammatory pathway, stimulating target gene expression, and producing a large number of inflammatory cytokines, such as tumor necrosis factor alpha (TNF- α), interleukin 1 (IL-1), and IL-6, which activate the ceramide pathway, thereby producing large amounts of sphingomyelinase and ceramide synthase and eventually causing more tissue damage and cell apoptosis; (2) fibronectin breakdown, which stimulates macrophages leading to activation of matrix metalloproteinases (MMPs); (3) impaired mitochondria produce more ROS, which activates NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome pathway. NLRP3 activates caspase-1, which produces IL-1 β and leads to apoptosis.

including nutritional intervention, pain control, prevention and/or treatment of secondary infection (32–35). Many studies have proved that nutritional intervention improves acute radiation-induced oral mucosal response of HNC patients. Nutritional intervention can effectively maintain the nutritional status of patients with HNC treated with RT and promotes recovery from acute RIOM. It has also been pointed out that the protein level in the body during RT also affects the severity of oral mucositis, and low protein levels have negative effects on RIOM healing (17). Therefore, a growing number of physicians focus on the effects of early nutritional intervention on RIOM and on the nutritional status of patients with HNC.

Malnutrition

The nutritional status of many HNC patients is at high risk of cachexia. RT or chemoradiotherapy also increases the risk of malnutrition. There is evidence that because of the location and treatment of the primary tumor, > 90% of patients have dysphagia, dry mouth, taste change, and oral mucositis, thereby affecting mouth opening and eating and resulting in symptoms of malnutrition (24, 36–38). Both acute and chronic malnutrition can lead to a decline in patients' quality of life (39). Malnutrition and cachexia, which affect the course of RT treatment of patients and increase the risk of early death of patients, are considered as poor prognostic factors for HNC patients undergoing RT. Undoubtedly, the side effects caused by RT to the head and neck are key factors for malnutrition in patients. However, many other factors are important for the occurrence of malnutrition, such as smoking and drinking, and even psychological stress (40). A recent study suggested that the polymorphism SELP-2028 C/T of the P-selectin adhesion molecule gene in HNC patients undergoing RT could be used as a risk factor marker for malnutrition. P-selectin adhesion molecule plays an important role in activating leukocyte recruitment, promoting tumor invasion, and cancer cachexia at the site of inflammatory injury. CC homozygotes are four times more likely to be diagnosed with severe malnutrition and have a

higher risk of early death than other genotype carriers (41). These results may provide the basis for early intervention in HNC patients undergoing RT.

Malnutrition has a huge effect on RT in patients with HNC. Therefore, it is necessary to assess the nutritional status during RT. Currently, the commonly used nutrition assessment tools include nutritional risk screening 2002 (NRS2002), malnutrition universal screening tool (MUST), mini nutrition assessment (MNA), and patient-generated subjective globe assessment (PG-SGA) (Table 1).

NRS2002 is a screening tool recommended by the European Society for Parenteral Nutrition (ESPEN) in 2002. It includes a disease severity score, an impaired nutritional status score, and an age score. If the three scores add up to > 3, the patient is at nutritional risk. With high reliability, NRS2002 can truly and objectively reflect the nutritional risk of tumor patients and is suitable for clinical use. It is a primary screening tool that has passed the evidence analysis standards of the American Association of Dietitians. The United States recommend NRS2002 for hospitalized patients with nutritional risk screening (42). NRS2002 is good for screening the nutritional status of elderly inpatients or cancer inpatients, especially for tumors affecting the digestive tract such as the oropharynx and esophagus (43). It has been reported that NRS2002 score is a simple and useful indicator for predicting long-term prognosis in patients with esophageal cancer after chemoradiotherapy (44). Peng et al. (45) screened 3,232 qualified patients to determine the application value of NRS2002 in patients with nasopharyngeal cancer. By analyzing the survival rate and quality of life of patients, they adjusted the NRS2002 screening tool and obtained a simpler and more clinically practical nutritional risk screening tool for nasopharyngeal cancer.

MUST was developed by the multidisciplinary malnutrition advisory group of the British association for parenteral nutrition and consisted of three assessments of body mass index (BMI), degree of body mass loss, and reduced dietary intake. A score > 2 indicates high nutritional risk. MUST is a simple and effective

TABLE 1 | The commonly used nutrition assessment tools.

	Composition	Assessment criteria
NRS2002	Disease score Nutritional status Age score	0–2: low nutritional risk >3: high nutritional risk, need nutrition intervention
MUST	BMI Weight loss Eating state	0: low nutritional risk 1: moderate nutritional risk 2: high nutritional risk, need nutrition intervention
MNA	Anthropometric assessment Global evaluation Dietetic evaluation Subjective assessment	≥24: normal 17–24: nutritional risk <17: malnutrition
PG-SGA	Weight loss Disease score Metabolic stress Physical examination Global assessment grading	A: normal B: nutritional risk C: severe malnutrition

NRS2002, nutritional risk screening 2002; MUST, malnutrition universal screening tool; MNA, mini nutrition assessment; PG-SGA, patient-generated subjective globe assessment; BMI, body mass index.

tool for nutritional risk assessment of cancer patients and has been widely accepted and effectively used by health professionals (46). In hospitalized cancer patients, MUST has the highest coincidence rate with NRS2002 and is a good identifier of patients at risk of prolonged hospitalization (47).

Developed according to subjective globe assessment, PG-SGA is a nutritional status assessment method specially designed for tumor patients and recommended by the American Dietitian Association. PG-SGA includes both patient self-assessment and medical personnel assessment. It is divided into three grades according to the obtained score: A, B, and C. Grades B or C indicate moderate or severe malnutrition, respectively. The incidence of malnutrition was high in patients with oral cancer before RT. Nutritional intervention for nasopharyngeal carcinoma patients undergoing concurrent chemoradiotherapy according to PG-SGA scores showed that the intervention significantly reduced acute radiation toxicity and improved patient nutritional status, quality of life, and treatment compliance (48). The use of PG-SGA to assess nutritional status before RT can be used as a prediction factor for RT response. PG-SGA nutritional score < 9 was associated with better local control and acute toxicity in patients undergoing radical head and neck cancer treatment (49). PG-SGA can also assess the nutritional status of patients with enteral nutrition and head and neck cancer treated with gastrostomy, especially in patients with impaired language skills (50).

MNA is a new evaluation method of human nutritional status established and developed by Vellas et al. (51–54) in the 1990s. It includes anthropometric measurements, overall evaluation, a dietary questionnaire, and subjective evaluation. The method is simple and shows good linear correlation with the human body composition evaluation method.

PG-SGA is more focused on the evaluation of chronic nutritional changes than NRS2002. MUST is specifically used to assess the risk of protein-calorie malnutrition with high accuracy and reliability. PG-SGA was significantly consistent with MNA, however, consistency between PG-SGA and NRS-2002 was moderate (55).

CLINICAL INTERVENTION FOR RIOM AND MALNUTRITION IN HNC PATIENTS

Medication

There is still no specific treatment for RIOM. To promote healing from RIOM, the treatment has been focused on relieving the pain and inhibiting oxidative stress and the inflammatory response in patients (**Table 2**). Anesthetics and analgesics are often administered to relieve the pain caused by RIOM. According to the evidence-based clinical practice guidelines on mucositis published by the mucositis research group of the Multinational Association of Support Care in Cancer/International Society of Oral Oncology (MASCC/ISOO), morphine mouthwash and doxepin mouthwash are recommended for HNC patients undergoing RT (33, 56, 57). Studies have also shown that introduction of low-dose controlled-release oxycodone in the early stage of moderate pain in patients with RT and chemotherapy for nasopharyngeal cancer can help to reduce total dose, provide better pain control, reduce weight loss, and improve quality of life (58–60). Anti-inflammatory therapy is also a common clinical treatment. The MASCC/ISOO mucositis guidelines have recommended the use of benzydamine mouthwash to prevent oral mucositis in HNC patients (61). A number of recent studies have also reported that some other drugs have been effective in reducing oxidative stress and inflammatory responses to RIOM. Rosiglitazone, a peroxisome proliferator activated-receptor (PPAR) gamma agonist stimulation drug, has anti-inflammatory and anti-fibrosis effects. It inhibits the growth of irradiation-induced transforming growth factor beta (TGF- β) and NF- κ B p65 subunit proteins and enhances the expression of catalase to protect the oral mucosa without affecting the efficacy of RT (62). Thalidomide, an NF- κ B inhibitor, significantly improved mucosal tissue in irradiated mice, although the underlying mechanism still requires further study (63). Other drugs, such as amiforstine and gliclazide, reduce oxidative stress and inflammation (64, 65). Growth factors and cytokines are also used to treat radiation mucositis. RT can induce apoptosis of proliferating basal cells, and growth factors such as epidermal growth factor and

TABLE 2 | Drugs commonly used to treat RIOM.

Drugs category	Drugs	Mechanism	Treatment effect	Reference
Analgesic drugs	Morphine and Doxepin mouthwash	Anesthesia and analgesia	Reduce the pain caused RIOM Increase eating	(33, 56, 57)
	Oxycodone			
Anti-inflammatory drugs	Benzydamine mouthwash	Local anti-inflammatory	Prevent RIOM	(61)
	Rosiglitazone	PPAR- γ agonists, Inhibition of TGF- β and NF- κ B p65 expression	Protect normal oral mucosa and antitumor	(62)
	Thalidomide	Inhibition of NF- κ B	Reduce inflammatory response	(63)
Cytogenetic drugs	amiforstine and gliclazide	Reduce oxidative stress and inflammation caused by 5-fluorouracil	Accelerate the recovery oral mucositis caused by 5-fluorouracil	(64, 65)
	epidermal growth factor and keratinocyte growth factor	promote the regeneration of oral mucosal cells	promote the healing of RIOM	(66, 67)
Others	Tat-smad7	Reduce TGF- β and NF- κ B signaling pathways	Reduce inflammatory response and promote the healing of RIOM	(68)
	multivitamin B + Gene Time(R)	Promote the synthesis of DNA, RNA and hydroxyproline	Shorten the healing time of ulcer	(69)

PPAR, peroxisome proliferator activated-receptor; TGF, transforming growth factor; NF- κ B, nuclear factor-kappa B; RIOM, radiation-induced oral mucositis.

keratinocyte growth factor (KGF) accelerate the conversion rate of epithelial cells and contribute to the regeneration of oral mucosal cells (66, 67). In addition, some drugs have been reported to promote healing of RIOM. Luo et al. (68) fused Smad7, multifunctional protein, with a cell-penetrating Tat tag (Tat-smad7), which was applied to the oral mucosa of RT mice at the onset of oral mucositis. The results suggested that short-term application of Tat-Smad7 promoted oral mucositis healing without affecting the cytotoxic effect of RT on cancer cells. Both multivitamin B and GeneTime (R) have been used in the treatment of oral inflammation. There is evidence that the combination of multivitamin B and GeneTime (R) is more effective for the treatment of RIOM and can reduce the healing time of ulcer (69).

Oral Health and Photobiomodulation Therapy (PBMT)

Although RIOM is not caused by pathogens, destruction of the mucosal barrier facilitates invasion of pathogens. Infection complicates the damage of mucositis. The abundance of a variety of gram-negative bacteria (*Fusobacterium*, *Haemophilus*, *Tannerella*, *Porphyromonas*, and *Eikenella*) in the oral mucosa may influence susceptibility of patients to RIOM (70). Therefore, oral health intervention is necessary. As a common superficial oral infection in cancer patients, *Candida* colonization in the oral mucosa may delay RIOM healing. Miconazole, an antifungal drug, is expected to reduce the length of hospital stay for RIOM and the use of morphine in patients (71). In addition, probiotics such as *Bacteroidetes* and *Bifidobacteria* can significantly increase the number and activity of immune cells and are beneficial for RIOM. Studies have shown that a combination of probiotics can significantly enhance the immune response of patients and reduces the severity of RIOM by changing the intestinal microbiota (72–74).

PBMT, which is recommended by MASCC/ISOO for tumor support therapy, can also be used to prevent and treat RIOM (75). PBMT can improve the quality of life, effectively control RIOM, and reduce the incidence and associated costs of RIOM (76, 77). Currently, the best studied PBMT includes low-level laser therapy (LLLT) and photodynamic therapy (PT). One study evaluated the efficacy of LLLT in the prevention and treatment of oral and oropharyngeal mucositis in patients with oral squamous cell carcinoma because of chemoradiotherapy. After 5 weeks of treatment, 72.7% of the mucosa in the laser group was normal (Grade 0), 20.0% of the control group was Grade 0, and 40.0% of the control group was Grade 2. The effect of LLLT in reducing the incidence and severity of mucositis is significant (78). Both LLLT and PT stimulate the expression of basic fibroblast growth factor, TGF- β , and platelet-derived growth factor. The increase in basic fibroblast growth factor and platelet-derived growth factor levels because of PT is more obvious than that because of LLLT, and the effect of PT appears to be more significant than that of LLLT (79).

Nutrition Intervention

HNC, especially head and neck squamous cell carcinoma, is usually found in advanced stages. The nutritional status of patients at the time of admission are affected to varying

degrees by chemoradiotherapy, which can also cause or aggravate malnutrition in patients. RIOM over Grade 3 can aggravate the degree of malnutrition in patients with locally advanced nasopharyngeal carcinoma during RT (80). Many studies have shown that nutritional intervention can not only reduce the risk and severity of RIOM and improve the nutritional status of patients with HNC, but also improve patients' tolerance to RT and quality of life and enhance treatment efficacy (81–83). The best application for nutritional intervention is through oral intake. Oral nutrition is the first choice in patients who can eat. However, because of complications such as oral mucositis caused by the tumor itself or chemoradiotherapy, a patient's swallowing function is greatly affected. Currently, the main nutritional interventions are enteral nutrition and parenteral venous nutrition. There are many complications of intravenous nutrition, and enteral nutrition including nasogastric tube feeding and gastrostomy feeding is highly recommended in the clinic. Corry et al. (84) studied the effects of gastrostomy and nasogastric tube feeding in HNC patients treated with RT or chemoradiotherapy. The authors found that patients who underwent percutaneous endoscopic gastrostomy gained significantly more weight than those fed through a nasogastric tube. However, after 6 months of treatment, there was no difference in weight gain between the two groups, and the associated costs were 10 times higher in the gastrostomy group than in the nasogastric tube group. The duration of enteral nutrition in the gastrostomy group was significantly longer than that in the nasogastric tube group although there was no significant difference in pulmonary infection rate between the two groups. Current nutritional interventions are mostly initiated when patients' food intake is affected, although the nutritional status cannot be significantly reversed during RT (80). Therefore, early nutritional intervention is attracting more attention. A study of the effectiveness of preventive percutaneous endoscopic gastrostomy (PEG) demonstrated that only 22% of patients lost > 10% of their initial body weight. The most common complication was a minor perioral infection associated with the use of proton pump inhibitors before PEG placement.

Early Nutritional Intervention

There are different views on the timing of nutritional intervention in clinical practice. Nutritional intervention usually begins when patients with RIOM or severe gastrointestinal reactions have restricted feeding. However, the nutritional status of patients is difficult to improve significantly. Some prospective studies have demonstrated the significant effects of early nutritional intervention on RIOM and nutritional status in HNC patients undergoing RT (85, 86). Early nutritional interventions can lead to higher serum albumin and hemoglobin levels in HNC patients (87). Plasma albumin, which reflects the level of human protein, is an important nutrient for human body. The amino acid produced by the breakdown of plasma albumin can be used for synthesis of tissue proteins, energy supply, or conversion to other nitrogenous substances. And the decrease in hemoglobin reflects deficiencies in many nutrients, such as iron and

vitamins (especially B12). Early nutritional intervention by a multidisciplinary nutritional support team improved body weight loss rate, mucositis, albumin level, and hospital length of stay, which might lead to better clinical outcomes (88). Therefore, early nutritional intervention may contribute to improve malnutrition of patients. Meng et al. (89) divided 78 cases of nasopharyngeal cancer patients into early nutritional intervention group and late nutritional intervention group respectively. Early nutritional intervention began at the beginning of chemoradiotherapy, while late nutritional intervention began when the side effects of RT were evident. Both groups had reduced weight at the end of chemoradiotherapy and 3 months later. However, 3 months after finishing chemoradiotherapy, the early group began to regain weight, while the late group continued to lose weight. The weight, BMI, albumin, and prealbumin levels in the early group were lower than those in the late group during and after radiation therapy. Early nutritional intervention can reduce the incidence and level of severe oral mucositis (90).

Systematic organization of early nutritional therapy in HNC patients is absolutely essential. Early nutritional intervention can not only prevent and treat RIOM, but also effectively improve the nutritional status of patients and improve their tolerance to chemoradiotherapy and overall survival rates (91). According to the PG-SGA score, the number of patients with good nutrition was higher in the early stage of treatment than in the late stage. In addition, many patients had to stop the course of RT because of RIOM and malnutrition. The benefits of early nutritional intervention for RIOM and malnutrition are also reflected in the lower incidence of RT interruption, which ensures smooth

treatment (85). There was a linear correlation between the percentage of weight loss in HNC patients and the days delayed in RT process from before the end of radiotherapy (92). Early nutritional interventions, including oral feeding, nasogastric tube, and gastrostomy, can significantly improve weight loss and the interruption/delay of radiotherapy process and reduce the probability of accidental hospitalization (87, 93–97). In patients with enteral nutrition contraindications, even early 7-day supplemental parenteral nutrition improved their body composition at nutritional risk in the absence of any relevant clinical complications (98). A prospective study by Wei et al. (86) divided 54 HNC patients into an early nutritional group and an advanced nutritional intervention group. The results showed that the incidence of oral mucositis was significantly lower in the early group than in the late group. The nutritional status of these patients was assessed at week 4 and week 7, and the weight and BMI declines were more pronounced in the late group than in the early group. Plasma albumin, hemoglobin, and prealbumin levels, and total lymphocyte counts were significantly lower in both groups after week 7 of RT.

These prospective studies show that early nutritional intervention improves oral mucositis and nutritional status of patients with head and neck malignant tumors who undergo chemoradiotherapy (Table 3). In addition, it prevents malnutrition-related complications in tumor patients, avoids the interruption of RT, and improves the long-term quality of life of patients, which has broad implications. Further research is required to support the use of early nutritional support in patients undergoing RT for HNC.

TABLE 3 | Influence of early nutritional intervention on patients with head and neck radiotherapy.

Author	Year	Patients		Treatment	Result	p
		ENG	CG			
Meng et al. (89)	2019	46	32	CRT	CT/CRT break:10.9% VS. 25.0% days of CRT delayed for toxicity: 2.2 ± 1.8 VS. 3.1 ± 3.2 rate of patients with unplanned hospitalizations:13.0% VS. 31.3% advanced oral mucositis (3, 4):13.0% VS. 21.9%	0.017 0.033 0.009 0.028
Paccagnella et al. (92)	2010	33	33	CRT	weight loss: $-2.4 \pm 8.2\%$ VS. $-9.6 \pm 8.1\%$ CT/CRT break:30.3% VS. 63.6% days of CRT delayed for toxicity: 4.4 ± 5.2 VS. 7.6 ± 6.5 rate of patients with unplanned hospitalizations: 16.1% VS. 41.4%	0.0077 0.007 0.038 0.030
Piquet et al. (96)	2002	45	45	RT	weight loss: $3.5 \pm 0.7\%$ VS. $6.1 \pm 0.7\%$ hospital admission for dehydration: 0% VS. 18.0%	<0.01 <0.01
Wang et al. (87)	2012	35	23	CCRT	weight loss: $-1.68 \pm 6.33\%$ VS. $-6.55 \pm 7.28\%$ CT/CRT break: 28.6% VS. 73.9% albumin level change: $-15.05 \pm 10.41\%$ VS. $-27.38 \pm 11.41\%$	<0.01 0.010 0.002
Wei et al. (86)	2020	28	26	CT/CRT	weight loss: $-5.64 \pm 2.54\text{kg}$ VS. $-8.77 \pm 1.61\text{kg}$ albumin level change: $-4.79 \pm 3.69\text{g/L}$ VS. $-7.09 \pm 3.39\text{g/L}$ hemoglobin loss: $-12.96 \pm 19.83 \text{g/L}$ VS. $-14.81 \pm 24.47 \text{g/L}$ advanced oral mucositis (3, 4):17.9% VS. 50.0%	<0.001 <0.001 <0.001 0.012
Iserning et al. (99)	2004	29	31	RT	weight loss: -0.4kg VS. -4.7kg NI are beneficial to global QoL	<0.001 0.009
González-Rodríguez et al. (97)	2020	135	39	RT	malnutrition: 31.9% VS. 69.5% emergency visits 0.75 VS. 1.1 episodes per patient hospitalizations: 29% VS. 59%	0.0001 0.021 0.044
Kono et al. (88)	2020	32	61	CCRT	Grade III mucositis: 25.0% VS. 70.0%	0.006

ENG, early nutritional intervention group; CG, control group; RT, radiotherapy; CRT, chemoradiotherapy; CCRT, concurrent chemoradiotherapy; NI, nutrition intervention; QoL, quality of life. Values of $p < 0.05$ were considered significant.

CONCLUSION

In conclusion, radiation-induced oral mucositis and malnutrition have a significant effect on the course and recovery in HNC patients treated with RT. Many studies have shown that early nutritional intervention improves oral mucositis and nutritional status of patients. Although a number of prospective randomized trials have been conducted worldwide to assess the effects of early nutritional interventions on quality of life in cancer patients, comparison and evaluation of the effects of different nutritional intervention timings on the nutritional status of HNC patients undergoing RT have not been reported. More in-depth research is still required.

AUTHOR CONTRIBUTIONS

Study concepts: ZZ. Study design: XZ. Data acquisition: QZ. Quality control of data and algorithms: YZ. Data analysis and interpretation: SL. Statistical analysis: ZL. Manuscript preparation: ZZ and LM. Manuscript editing: YX and XJ.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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