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ORIGINAL ARTICLE

Nutri-jelly may improve quality of life and decrease tube feeding demand in head and neck cancer patients

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Abstract
Purpose Eating difficulty is a critical and common problem in head and neck cancer patients undergoing radiotherapy (RT). It leads to poor quality of life and extensive tube feeding use. Nutri-jelly, a food gel with semisolid texture, water-releasing ability, and ready-to-eat by spoon, was recently developed to alleviate the trouble. However, its efficacy was unknown. This study investigated the potential effect of Nutri-jelly on health-related quality of life (HRQOL) and nasogastric tube feeding use.
Methods A prospective quasi-randomized patients-preference controlled trial was conducted in 74 head and neck cancer patients. Subjects in study and control groups (37 each) had similar baseline HRQOL and body mass index and undergone definitive radiotherapy (25–35 RT fractions, 5,000–7,000 cGy). Only study group received a 200-ml box of Nutri-jelly as daily supplement throughout radiotherapy. HRQOL was scored by validated questionnaires. The use of tube feeding was collected from medical records.
Results From 11 to 35 RT fractions, the study group maintained higher overall HRQOL score than that of control group ($p<0.0001$). Multiple physiologic and psychological aspects of HRQOL especially swallowing difficulty and overall eating problems were significantly improved in study as compared to control group. Promisingly, the percentage of tube feeding use in study group (13.5 %) was dramatically lower than control group (48.6 %).
Conclusions Continuous supplementation of Nutri-jelly throughout radiotherapy may improve HRQOL and reduce tube feeding demand in head and neck cancer patients who preferred to take them. Nutri-jelly could be an alternative for head and neck cancer patients who have eating difficulty during radiotherapy.

Keywords Head and neck cancer · Clinical trial · Radiotherapy · Side effects · Quality of life · Dietary management · Dysphagia

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Introduction

Radiotherapy (RT) is among the most effective treatments for head and neck cancer. However, many patients suffer from side effects, posting challenges in treatment success. Common adverse consequences include oral mucositis, mouth pain, dry mouth, taste loss, difficulty in mouth opening (trismus), and fibrosis of pharyngeal muscles [1]. Furthermore, the patients often lose numerous teeth during pre-radiation mouth preparation. These lead to difficulties in chewing and swallowing, malnutrition, poor quality of life, and poor response to treatment [2–6]. Currently, tube feeding is a standard nutritional intervention leading to significant improvement in body weight [7]. Unfortunately, the procedure was invasive, and its effect on quality of life and mortality was inconsistent [8]. Furthermore, extended hospitalization due to tube feeding leaves burden to caregivers and increases risk of aspiration pneumonia and mortality [9]. Therefore, new noninvasive approaches to overcome the eating difficulty are essential [10].

In recent years, oral nutritious supplements have gained much of attention and proven to reduce weight loss [11]. Meta-analysis showed that oral supplementation with nutritious substances can improve certain aspects of life's quality but have no effect on patients' survival [12]. Currently available oral nutritional supplements are in powder and liquid forms. However, the powder forms are not ready to eat, and the liquid form is not adequate to stimulate mastication and oral swallowing. Limited oral muscular movement in tube-fed patients could decrease salivary flow and quality, reduce oral clearances, and increase bacteria colonization and risk of oral diseases [13, 14]. Although thickened liquid had been used in treatment of dysphagia for decades, oral dehydration is a common side effect from this intervention [15]. Therefore, its application in patients with xerostomia was limited. Furthermore, most people feel completely sick while on liquid diet. And, feeling ill is a predictor of poor survival in head and neck cancer [16]. Therefore, the ideal oral supplement for cancer patients should be ready-to-eat, most resemble to regular food (solid-like), chewable, moisten, and easy to swallow.

Recently, Nutri-jelly was successfully developed by collaboration of various experts. This product is a ready-to-eat nutritious gel with 230–260 kcal per serving (1 kcal/1 ml). It has solid appearance but can be melted under oral environment temperature [17]. Upon biting or spooning, the food gel will release some water due to syneresis [18]. Optimum gel texture was identified and proved easily to swallow by 95 % of 115 head and neck cancer patients suffering from eating troubles [17]. Furthermore, 80 % of 120 patients were satisfied with the texture, flavor, and moisture of Nutri-jelly [17]. Although it was proved edible by head and neck cancer patients, its benefit to quality of life and its impact on tube feeding demand were unknown.

The purpose of this study was to investigate the potential effect of Nutri-jelly on health-related quality of life (HRQOL) and nasogastric (NG) tube feeding use in head and neck cancer patients undergoing definitive radiotherapy.

Methods

Intervention

Nutri-jelly products were provided by the Dental Innovation Foundation under Royal Patronage. The product was certified by Thai Food and Drug Administration (FDA) and HALAL. It was manufactured in ultra-high temperature (UHT) processing and aseptic filling system by Ampol Food Processing Co., Ltd under international standard (Good Manufacturing Practice (GMP), Hazard Analysis and Critical Control Points (HACCP), and International Organization for Standardization (ISO) 22000). The shelf-life at room temperature is 1 year. There are two flavors: Thai tea and mango (Fig. 1a). The product has semisolid texture, water-releasing ability, and is ready-to-eat by spoon (Fig. 1b). One serving (one box) contains 230 kcal (Thai tea flavor) and 260 kcal (mango flavor). The nutrition fact of each flavor was shown in Fig. 1c. Each 1 g of Nutri-jelly contains 1 kcal. Sources of energy were from carbohydrate, fat, and protein in the ratio of 50:30:20, respectively.

Participants

Inclusion criteria were as follows: being diagnosed with head and neck cancer patients with International Classification of Disease (ICD) 10, C00–C14 and C31–C32 and undergoing definitive radiotherapy (25–35 (RT) fractions, 5,000–7,000 centigrays (cGy) with Cobalt-60 radiation. Exclusion criteria were as follows: having active oral bleeding, difficult breathing, extremely poor life's quality (baseline HRQOL score <4), and being unable to make reliable decision or effective communication. All subjects signed their written informed consent prior to inclusion in the study. Their identities have been protected.

Sample size calculation

The estimated sample size was identified by priori power analysis using G Power 3.1 [19]. The effect size was calculated from pilot data (mean overall HRQOL and standard deviation (SD) of ten control subjects at baseline (0–5 RT), 6–10, 11–15, 16–20, 21–25, and 26–35 RT fractions. Based on analysis of variance, we need to enroll 24 subjects per group to achieve 90 % power at a two-sided 1 % significance level. To account for an up to 30 % dropout rate, at least 32 patients were required in each group. Initially, 80 patients agreed to be enrolled in the study. Finally,

a

b

c

Nutrition fact **Nutri-jelly (mango flavored)** Serving size: 1 (250 ml, 235.5g) Servings per container: 1 Total energy per serving 260 kcal (energy from fat 70 kcal)		Nutrition fact **Nutri-jelly (milk tea flavored)** Serving size: 1 (250 ml, 235.5g) Servings per container: 1 Total energy per serving 230 kcal (energy from fat 60 kcal)	
	Percent Thai RDI*		Percent Thai RDI*
Total fat 8 g	12 %	Total fat 7 g	11 %
Saturated fat 2.5 g	12 %	Saturated fat 2 g	10 %
Cholesterol 30 mg	10 %	Cholesterol 15 mg	5 %
Protein 11 g		Protein 10 g	
Total carbohydrate 37 g	12 %	Total carbohydrate 32 g	11 %
Dietary fiber 1 g	4 %	Dietary fiber <1 g	3 %
Sugars 24 g		Sugars 9 g	
Sodium 115 mg	5 %	Sodium 140 mg	6 %
Vitamin A	15 %	Vitamin A	10 %
Vitamin B	20 %	Vitamin B	25 %
Iron <	2 %	Iron	0 %
Vitamin B1	10 %	Vitamin B1	8 %
Calcium	30 %	Calcium	30 %
* Thai RDI for persons at the age of 6 years old and over, energy requirement of 2000 kcal/day			

Fig. 1 Nutri-jelly. **a** The packages of Nutri-jelly in UHT brix: mango flavor (*yellow label*) and milk tea flavor (*brown*). **b** Texture of Nutri-jelly is semisolid (*left image*). Upon cut or bitten, water will be released from the gel (*middle image*). The patients on NG tube feeding can eat it with spoon, like regular food (*right image*). **c** Nutrition fact of mango- and milk-tea-flavored Nutri-jelly. One serving contains 260 or 230 kcal as shown. The percentages of nutrient are based on Thai RDI

completed data were from 74 patients (92.5 %) composing of 37 patients in study group and 37 patients in control groups.

Study procedures

This study was approved by the institutional ethics committee for research in human of Mahavachiralongkorn Cancer Hospital and performed according to the Declaration of Helsinki. As the first study to investigate the possible benefit of Nutri-jelly, adherence to Nutri-jelly intake during 5–7 weeks of RT was absolutely required. In clinical trials, evidences showed that patients who received their preferred treatment might be better motivated, complied with treatment program, and report more reliable outcomes [20]. Therefore, in this study, we used a prospective quasi-randomized patient-preference trial (PPT) design [20]. Patients who passed the inclusion criteria and signed the written informed

consent were assigned to study or control groups based on their preference for continuous Nutri-jelly intake. To prevent selection bias and avoid ethical issues, all subjects had equal chance to try a few spoon of Nutri-jelly at the beginning (0–5 RT fractions, before having any complications from RT). Patients who accepted and rejected to continuously take Nutri-jelly were assigned into study and control groups, respectively. The reasons for rejection were unsatisfied to taste and appearance. Baseline HRQOL, baseline body mass index, and demographic characteristics of patients in study group were compared with those of control group to ensure that both groups were homogeneous. The study group received radiotherapy and a 200-ml box of Nutri-jelly as daily supplement throughout radiation course (5–7 weeks). In contrast, the control group received only standard radiotherapy. Their HRQOL scores were assessed at every 5 RT fractions. The study was single-blinded for outcome assessor.

Outcome measure

The primary outcome was HRQOL. The secondary outcome was percentage of tube feeding use.

Health-related quality of life assessment

HRQOL scores were assessed at every 5 RT fractions (once a week for 5–7 weeks). Thus, the tool should be informative but as concise as possible. Unfortunately, widely accepted questionnaires such as European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) with Head and Neck cancer (H&N 35) or Functional Assessment of Cancer Therapy—Head and Neck (FACT-HN) contain excessive questions (65 and 39 items, respectively), which was not feasible for weekly assessment of patients during radiotherapy. Therefore, we developed a new 14-item questionnaire and validated it in head and neck cancer patients. This tool aimed to evaluate physiologic, psychologic, and social aspects of HRQOL, as previously published [5, 21]. However, this questionnaire only included physiologic domains strongly associated with weight loss as reported [22] and common psychosocial problems for head and neck cancer patients suggested by experienced caregivers. The tool included 14 questions asking how bothersome of each problem. The problem score ranged from 0 (no problems) to 10 (most troublesome). The HRQOL score of each domain was the subtraction of averaged problem score from ten. Overall HRQOL score of each subject was calculated as the mean of all domain scores. Content validation was analyzed by Lynn method [23]. Five evaluators included dentist, radiation oncologist, oncology nurse, nutritionist, and expert in quality of life measurement. The questionnaire was revised until all experts gave favorable score to all items (≥3 out of score 5). The final version had content validation index of 1 and reliability index (Cronbach's alpha) of 0.9. The questionnaire was shown in Online Resource.

Tube feeding use

Before starting the trial, none of patients in both groups had used tube feeding for nutritional supports. During radiotherapy, admission for NG tube feeding was obtained from medical records. Percentage of tube feeding in study and control groups was calculated from the number of patients receiving tube feeding during radiotherapy compared to all patients in their respective groups.

Statistical analysis

Sample size and power were calculated by G Power 3.1. Graphing and statistical analysis were performed by GraphPad Prism 5.0. Normality of data distribution was verified by D'Agostino and Pearson omnibus test. Parametric statistical tests were used only when the data passed normality test ($p>0.05$). Comparison of baseline quality of life (overall and domain-specific), age, and domain-specific health-related quality of life scores in study and control groups was analyzed by independent *t* test. Comparison of their baseline body mass index (BMI) and certain domain-specific health-related quality of life scores was analyzed by Mann-Whitney test. Comparison of categorical data between study and control groups (e.g., frequency in tube feeding use, baseline demographic data, etc.) was analyzed by chi-square or Fisher's exact test. Changes of overall HRQOL score over time of radiation were analyzed by one-way ANOVA and Bonferroni test. Comparison of overall HRQOL between study and control groups at various time points was analyzed by two-way ANOVA and Bonferroni test. All tests were performed with two-tailed, $\alpha=0.05$. A p value <0.05 was considered statistically significant. At the end, post hoc power analysis was performed to confirm that the sample size was enough to gain at least 90 % power of for all test.

Results

Baseline data

Initially, 80 patients were enrolled. Then, six patients were dropped out (four from control group and two from study group) due to loss of follow-up and incomplete data. Finally, completed data were from 74 patients (92.5 % retention) composing of 37 patients in study group and 37 patients in control groups.

All baseline demographic data and illness characteristics of both groups were not different ($p>0.05$) (Table 1). Baseline overall HRQOL scores in study and control groups were relatively similar (7.52 and 7.73, respectively, $p=0.73$).

Table 1 Characteristics of patients in study and control groups

Characteristic		Study group (n=37)			Control group (n=37)			p value
		N	%	Mean±sd.	N	%	Mean±sd.	
Baseline overall quality of life				7.52±1.35			7.73±1.8	0.73[a]
Baseline body mass index (BMI)				22.09±4.87			21.58±5.16	0.58[b]
Age				56.95±10.92			53.7±12.66	0.24[a]
Sex	Male	26	70.27		24	64.86		0.80[c]
	Female	11	29.73		13	35.14		
Marital status	Single	9	24.32		8	21.62		0.78[d]
	Married/widow/divorced	28	75.68		29	78.38		
Religion	Buddhism	35	94.59		35	94.59		1.00[c]
	Christ/Islam	2	5.41		2	5.41		
Education	Primary school	25	67.57		22	59.46		0.77[d]
	Secondary school	8	21.62		10	27.03		
	Undergraduate and graduate	4	10.81		5	13.51		
Occupation	Physically active (agriculture, laborer)	15	40.54		13	35.14		0.81[c]
	Nonphysically active (unemployed, housewife, monk, retired, government, business,)	22	59.46		24	64.86		
Monthly income	<5,000 baht	21	56.76		20	54.05		0.92[d]
	5,000–20,000 baht	13	35.14		13	35.14		
	>20,000 baht	3	8.11		4	10.81		
Health insurance	National health care	29	78.38		31	83.78		0.75[d]
	Social insurance/government benefit	7	18.92		5	13.51		
	Self-payment	1	2.70		1	2.70		
Primary site	Lip/oral cavity/oropharynx	18	48.65		18	48.65		0.81[d]
	Nasopharynx/maxillary sinus	9	24.32		11	29.73		
	Other head and neck areas	10	27.03		8	21.62		
Clinical stage	Early (I–II)	7	18.92		9	24.32		0.78[c]
	Late (III–IV)	30	81.08		28	75.68		
Previous treatment of cancer	None	23	62.16		21	56.76		0.87[d]
	Surgery	11	29.73		12	32.43		
	Radiotherapy/chemotherapy	3	8.11		4	10.81		
Treatment plan	Concurrent chemoradiotherapy	4	10.81		5	13.51		0.72[c]
	Radiotherapy only	33	89.19		32	86.49		
Radiation dose	7,000 cGy (35 fractions)	30	81.08		30	81.08		1.00[c]
	3,600–6,000 cGy (18–30 fractions)	7	18.92		7	18.92		

[a] p value from independent t test

[b] Mann-Whitney test

[c] Fishers' exact test

[d] Chi-square test

Analysis of domain-specific HRQOL showed that baseline HRQOL scores of all domains in both groups were similar (Table 2). As shown in Table 1, at baseline, BMI in both groups was quite similar (22.09 and 21.58, respectively, p=0.58) and considered as normal nutrition status for Thai healthy adults (BMI, 18–25). Therefore, at baseline, none of the patients required NG tube feeding. Most of the participants in both study and control groups were male Buddhists with average age of 56.95 and 53.7 years, respectively. Most of them were married and graduated from primary school. More than half of them were unemployed or having nonphysically active jobs with monthly income less than 5,000 Thai baht. The cancer treatment expense of most patients in both groups was covered by National health care plan which was totally free of charge. Almost half of patients were diagnosed with primary lip/oral cavity or oropharyngeal cancer, while the rest had cancer in nasopharynx and other area. A majority of patients in both group had cancer in late stage, and more than half of them had never been treated. Most of patients in both groups would receive definitive radiotherapy only, while a small number (10.81 and 13.51 %, respectively) would receive concurrent chemoradiotherapy. Eighty-one percent of

Table 2 Baseline quality of life in study and control groups: domain specific

Domain	Study group (mean±sd)	Control group (mean±sd)	*p* value*
Mouth pain	7.19±2.45	8.35±2.69	0.18
Burning mouth	8.77±1.88	8.92±2.66	0.36
Swallowing difficulty	6.50±3.18	6.42±4.13	0.83
Dry mouth	6.00±3.13	7.30±3.16	0.22
Trismus	7.16±2.98	6.81±3.69	0.73
Taste alteration	6.04±2.96	6.58±3.68	0.60
Overall eating problems	6.08±3.24	6.60±3.70	0.59
Mouth odor	8.62±2.22	9.43±1.50	0.21
Tired easily	7.77±2.45	6.85±2.93	0.14
Fatigue	8.08±2.17	7.54±2.07	0.47
Discouraged	8.71±2.45	9.54±1.13	0.47
Limited daily activity	6.92±3.77	6.95±3.47	0.97
Social isolation	9.12±1.96	9.15±1.86	0.97
Appearance	8.81±2.29	7.92±3.18	0.69

*The significance of differences was statistically tested by independent *t* test

patients in both groups would receive 7,000 cGy of Cobalt-60 radiation, which required 35 RT fractions and 7 weeks treatment period.

Effect of Nutri-jelly on overall health-related quality of life

To evaluate the effect of Nutri-jelly on quality of life, changes in overall HRQOL score of study group were compared with those of control group. As shown in Fig. 2a, after receiving radiotherapy, the average overall HRQOL score in the control group significantly decreased in a dose-dependent manner ($p<0.0001$). Bonferroni post hoc test showed that the significant differences in HRQOL compared to baseline score were found from 16 to 35 fractions of RT (3,200–7,000 cGy). This suggested that overall quality of life in head and neck cancer patients was reduced over time during radiotherapy. In contrast, in Fig. 2b, the average overall HRQOL scores in study group were not significantly different from baseline throughout the study ($p=0.8891$). In Fig. 2c, comparative analysis between study and control groups showed that at the beginning (0–5 RT fractions) before receiving Nutri-jelly, the mean overall HRQOL scores of both groups were not different (7.5 vs 7.73, respectively, $p>0.05$). However, after receiving 11–35 fractions of RT, the overall HRQOL score in study group was significantly higher than that of the control group ($p<0.0001$). The highest significant difference was found at 26–35 RT fractions, which was the last period of treatment. This data suggests that continuous intake of Nutri-jelly during definitive radiotherapy may improve overall health-related quality of life in head and neck cancer patients.

Effect of Nutri-jelly on domain-specific health-related quality of life

Since the difference in overall HRQOL score between study and control groups was significant during 11–35 fractions of RT, we further identified which specific domains of HRQOL could be improved by Nutri-jelly. In Table 3, means of each domain scores in study and control groups were compared. Interestingly, from 11 to 20 fractions, there were several physiologic domains with significantly better score in the study group at certain time points. These included mouth pain, swallowing difficulty, dry mouth, trismus, taste alteration, and overall eating problems. In addition to those domains, from 21 to 35 RT fractions, some more physiologic domains were improved in the study group, i.e., burning mouth, mouth odor, tired easily, fatigue, and interference with daily activities. Also, psychological domain such as discouraged was improved during this period. Importantly, the domains that significantly improved at all time points of radiation were swallowing difficulty and overall eating problems. The most striking differences between study and control groups were found in 26–35 RT fractions in which HRQOL score of almost all domains became significantly better. In contrast, there were no significant changes of social domains such as social isolation and confidence in appearance in both study and control groups. These data suggested that continuous intake of Nutri-jelly may improve physiologic and psychological aspects of HRQOL in head and neck cancer patients, during the middle and late phases of radiotherapy (11–35 RT fractions).

Effect of Nutri-jelly on tube feeding use

At baseline (0–5 RT fractions), average BMI of patients in both groups indicated normal nutritional status, and none of the patients received NG tube feeding. As shown in Table 4, during radiotherapy (6–35 RT fractions), there were 48.6 % of patients in control group admitted for NG tube feeding, while only 13.5 % of patients in the study group were tube-fed. Statistical analysis demonstrated that the difference was highly significant ($p=0.0045$). Taken together, these data suggested that continuous intake of Nutri-jelly during RT may decrease hospital admission for NG tube feeding.

Discussion

Eating difficulty is a critical problem in head and neck cancer patients since it could lead to malnutrition, poor quality of life, and poor treatment response [24, 25]. Nutritional status is a strong predictor for quality of life in cancer patients before and after treatment [26–28]. Nutritional intervention such as tube feeding was found to improve overall quality of life; however,

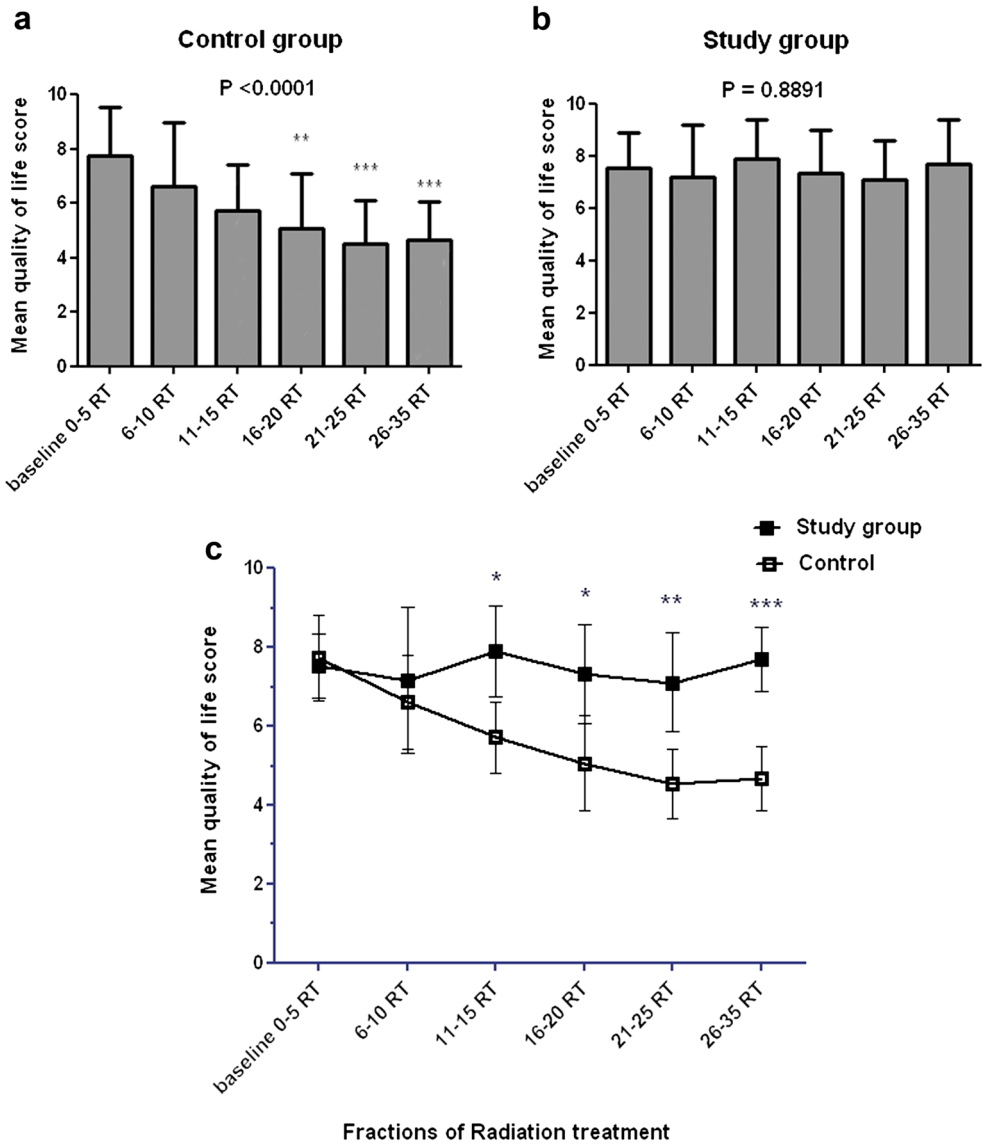

Fig. 2 Effect of Nutri-jelly intake during radiotherapy on overall HRQOL. **a**–**b** Changes of HRQOL scores during RT in control group (**a**) and study group (**b**). Each *bar* represented mean quality of life score at different time of RT. *Error bars* indicated standard deviation (SD). One-way ANOVA test showed significant difference in control group ($p<0.0001$) and no significant difference in study group ($p=0.8891$). Bonferroni test identified time points with significant difference from baseline. **c** Comparison between study and control group. Each point represented mean quality of life score at different time of radiotherapy. *Error bars* indicated standard deviation (SD). Control group (radiotherapy only) (*white square*); study group (radiotherapy and one box of Nutri-jelly/day) (*black square*). Two-way ANOVA showed difference ($p<0.0001$), followed by Bonferroni test. *$p<0.05$; **$p<0.01$; ***$p<0.001$

the procedure is invasive [29]. Furthermore, deprivation of chewing and swallowing contributed to distress in tube-fed patients [30]. Using prospective quasi-randomized patient-preference trial design with control group comparison, here, we reported that continuous supplementation of Nutri-jelly throughout radiotherapy may improve HRQOL and reduce tube feeding demand in head and neck cancer patients who preferred to take them. The promising result renders us to pursue further randomized studies. Systemic reviews suggest that random allocation of patients with preferences into study or control group may affect the internal validity and outcome of the controlled trial [31]. Therefore, future randomized controlled study should be performed in patients who preferred to take Nutri-jelly.

Unlike many other oral supplements, Nutri-jelly is ready-to-eat, solid-like, moisten, chewable, and easy to swallow [17]. These properties make it suitable for patients with eating difficulty and dry mouth such as cancer patients undergoing radiotherapy. Since swallowing ability and overall eating were the domains of HRQOL most significantly improved by Nutri-jelly, the favorable outcome in overall HRQOL likely resulted mainly from increased oral intake. Consistently, previous studies reported that ingestion of oral nutritional supplements could improve certain aspects of quality of life [12]. However, currently marketed supplements still could not improve patients' survival [12]. Here, Nutri-jelly was found to improve multiple domains of HRQOL including swallowing, mouth pain, and discouragement. Coincidentally, these exact domains were reported as good predictors for survival of head and neck cancer patients [16]. This result encourages further investigation of the effect of Nutri-jelly on survival of cancer patients.

From 16 to 35 fractions of RT (3,200–7,000 cGy), subjects in the control group had significant decrease in overall

Table 3 Domain-specific health-related quality of life score

Domain	11–15 RT fractions			16–20 RT fractions			21–25 RT fractions			26–35 RT fractions		
	Study group	Control group	*p* value*	Study group	Control group	*p* value*	Study group	Control group	*p* value*	Study group	Control group	*p* value*
Mouth pain	5.22	3.56	ns	6.44	3.04	0.011	5.00	1.70	0.004	5.00	2.93	0.043
Burning mouth	6.22	4.06	ns	6.44	5.75	ns	5.75	1.93	0.003	6.63	3.18	0.002
Swallowing difficulty	6.78	3.27	0.005	5.28	2.79	0.025	5.69	1.93	0.0006	6.18	3.21	0.006
Dry mouth	7.00	3.28	0.004	5.67	4.32	ns	5.81	2.30	0.002	5.36	3.14	0.031
Trismus	8.28	5.34	0.024	7.33	5.43	ns	7.19	6.07	ns	7.16	4.54	0.022
Taste alteration	8.83	4.41	0.001	5.67	4.17	ns	5.25	2.60	0.030	7.24	2.93	0.0003
Overall eating problems	5.67	3.25	0.045	5.89	1.71	<0.0001	4.19	1.27	0.005	5.97	2.36	0.001
Mouth odor	8.89	7.31	ns	8.56	7.29	ns	8.13	6.80	ns	8.58	6.43	0.049
Tired easily	9.11	7.13	ns	8.44	6.39	ns	8.94	5.80	0.024	9.39	5.00	<0.0001
Fatigue	8.00	7.00	ns	8.00	6.43	ns	8.50	5.73	ns	9.37	5.43	<0.0001
Discouraged	9.56	7.81	ns	9.33	7.00	ns	9.88	6.80	<0.0001	9.74	6.38	0.0004
Limited daily activity	7.89	5.56	ns	7.44	4.82	ns	7.25	4.53	ns	8.81	3.85	<0.0001
Social isolation	9.67	9.00	ns	8.11	6.21	ns	8.13	6.93	ns	8.40	7.57	ns
Appearance	9.44	8.63	ns	9.78	8.57	ns	9.75	8.40	ns	9.68	8.43	ns

The table shows mean of HRQOL scores in each domain at different time points of radiotherapy, comparing that of study group and control group

ns not statistically significant ($p>0.05$)

*The significance of differences was statistically tested by independent *t* test. At the points where statistical significance was found ($p<0.05$), the *p* values were shown

HRQOL. This was mainly due to decrease in scores of oral physiologic domains such as mouth pain, burning, taste loss, trismus, and dry mouth. Consistently, these RT doses are known to cause oral side effects including oral mucositis, loss of tongue papillae, muscle fibrosis, and acinar cell death in salivary glands [1, 32]. Therefore, the decline in overall HRQOL was likely due to those oral sequelae of radiation. Importantly, these could lead to chewing and swallowing difficulty, and poor quality of life [33]. In contrast to the control group, subjects in the study group could maintain HRQOL score of those oral domains throughout RT, without significant decrease. This might explain the observed effect of Nutri-jelly in improving swallowability and overall eating domains at all time points of radiation.

Our study exploited "standard therapy with no intervention" as the control group. Therefore, all patients of both groups inevitably recognized whether they took Nutri-jelly. Since low eating ability was correlated with depression [34, 35], realizing that they can eat Nutri-jelly by mouth may encourage the patients in study group to better tolerate treatment side effects. Although they may have similar oral conditions as control group, they might feel less bothered by those problems. Thus, the observed improvement in HRQOL may partly result from psychological effect of Nutri-jelly.

Based on the data, Nutri-jelly may significantly improve swallowing difficulty and overall eating domains of HRQOL. The mechanism for this effect probably results from its unique physical properties. Compared to currently available nutritional supplements, Nutri-jelly has solid-like appearance, more resembling to regular food. Furthermore, the syneresis property (water released from gel upon biting or spooning) of Nutri-jelly might rehydrate the dry mouth of patients, overcoming the limitation of those thickened liquid used in dysphagia treatment [15]. Future randomized controlled trial comparing Nutri-jelly with marketed liquid food products is warranted to confirm this hypothesis. Also, stimulation of salivary flow rate should be measured in the future study.

Nutri-jelly has 230–260 kcal/box, considered as a nutritional supplement. Therefore, it is not intended to replace NG tube feeding. Instead, it rather prevents or delays the need of NG tube use. In control group of this study, increasing dose of radiation resulted in oral dysfunction and eating impairment, evidenced by a significant decline in overall eating domain of HRQOL score. Inadequate oral intake leads to weight loss, malnutrition, and eventually requirement for NG tube feeding

Table 4 Nasogastric (NG) tube feeding use during definitive radiation therapy

	Study group	Control group	*p* value*
NG tube feeding	5 (13.5 %)	18 (48.6 %)	
Self-oral intake	32 (86.5 %)	19 (51.4 %)	
Total	37 (100 %)	37 (100 %)	0.0045

*The significance of differences between study and control groups was statistically tested by Fishers' exact test

[36]. In contrast, the study group received Nutri-jelly as supplement from the beginning until the end of RT. Even when their ability to eat regular diet was impaired, most of them could still eat edible soft diet supplemented by Nutri-jelly, thereby maintaining overall eating HRQOL score. This notion is based on a parallel study by Karapoch et al. that during radiotherapy, the study group exhibited less percentage of weight loss than control group due to better maintenance of overall dietary intake [37]. These findings might explain how Nutri-jelly supplement may reduce tube-feeding demand.

A study commented that oral intake while wearing NG tube feeding may be possible [38]. However, there are no supporting evidences in cancer patients. Here, we observed that a few patients in study group could still take Nutri-jelly orally while wearing the tube. Interestingly, their HRQOL scores were better than NG-tube-fed patients in control group (during 6–15 RT: average of 8.7, compared to 6.7, and during 20–35 RT: average of 6 compared to 4.8). Since preventive chewing and swallowing exercises may accelerate restoration of eating ability after tube removal [39]. Further studies are warrant to investigate the effect of Nutri-jelly on HRQOL and swallowing recovery in NG tube-fed patients.

Eating difficulty is found not only in cancer patients but also in other groups such as dental disease, tooth loss, jaw surgery, stroke, and Parkinson's disease [40]. Thus, Nutri-jelly may benefit to a broad range of patients. In conclusion, Nutri-jelly is a new oral nutritional supplement with potential clinical application, deserving further exploration.

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