Randomized double-blind, placebo-controlled trial evaluating oral glutamine on radiation-induced oral mucositis and dermatitis in head and neck cancer patients

Chih-Jen Huang,1,2 Ming-Yii Huang,1,2 Pen-Tzu Fang,1 Frank Chen,1 Yu-Tsang Wang,3 Chung-Ho Chen,4 Shyng-Shiou Yuan,4 Chun-Ming Huang,1,2 Kuei-Hau Luo,5 Hung-Yi Chuang,5,6 Yen-Yun Wang,5 and Hsin-Hua Lee1,7

1Division of Radiation Oncology, Department of Radiation Oncology; 2Faculty of Medicine, College of Medicine; 3Department of Medical Research; 4Faculty of Dental Hygiene; 5Department of Occupational and Environmental Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; 6Faculty of Department of Public Health, College of Health Science, Kaohsiung Medical University, Kaohsiung, Taiwan; and 7PhD Program in Environmental and Occupational Medicine, Kaohsiung Medical University and National Health Research Institutes, Kaohsiung, Taiwan

ABSTRACT

Background: Glutamine is the primary fuel for the gastrointestinal epithelium and maintains the mucosal structure. Oncologists frequently encounter oral mucositis, which can cause unplanned breaks in radiotherapy (RT).

Objectives: The aim of this study was to explore the association between oral glutamine and acute toxicities in patients with head and neck cancer undergoing RT.

Methods: This was a parallel, double-blind, randomized, placebo-controlled Phase III trial conducted in a university hospital. A central randomization center used computer-generated tables to allocate interventions to 71 patients with stages I–IV head and neck cancers. The patients, care providers, and investigators were blinded to the group assignment. Eligible patients received either oral glutamine (5 g glutamine and 10 g maltodextrin) or placebo (15 g maltodextrin) 3 times daily from 7 d before RT to 14 d after RT. The primary and secondary endpoints were radiation-induced oral mucositis and neck dermatitis, respectively. These were documented in agreement with the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.

Results: The study included 64 patients (placebo n = 33; glutamine n = 31) who completed RT for the completers’ analysis. Based on multivariate analysis, glutamine had no significant effect on the severity of oral mucositis (OR: 0.3; 95% CI: 0.05, 1.67; P = 0.019). Only the change in body mass index (BMI) was significant in both multivariate completers (OR: 0.41; 95% CI: 0.20, 0.84; P = 0.015) and per-protocol analysis (OR: 0.40; 95% CI: 0.20, 0.83; P = 0.014). No difference was found in the incidence and severity of neck dermatitis between the two arms.

Conclusions: The decrease in BMI was strongly related to the severity of oral mucositis in the head and neck cancer patients under RT, but not to the use of glutamine. This trial was registered at clinicaltrials.gov as NCT03015077.

Keywords: glutamine, mucositis, dermatitis, radiotherapy, BMI

Introduction

Patients with head and neck cancers generally receive multidimensional treatment, during which their quality of life is the chief concern (1, 2). Oncologists frequently encounter oral mucositis, which can be severe and cause hospitalization or unplanned breaks in radiotherapy (RT) (3, 4). Nearly all patients with head and neck cancer who receive chemotherapy and cumulative radiation doses of >30 Gy to the oral mucosal fields will develop mucositis (5). With or without chemotherapy, the incidence of radiation-induced oral mucositis is 80–91% (6, 7). In addition to the economic costs caused by treatment-related side effects (8), there is also a significant impact on the general well-being of cancer patients, who experience increased morbidity and mortality (9, 10).

Nonpharmacologic approaches for the prevention of oral mucositis, including glutamine and several other agents, have been investigated (11), although there is inadequate evidence confirming the advantage of glutamine as the research results
have been inconsistent (3, 12). Most studies have not been double-blind, randomized, placebo-controlled trials (RCTs). Glutamine, an oxidizable substrate, is the primary fuel for the gastrointestinal epithelium and maintains the mucosal structure (13–15). Human cancer cell lines exhibit a 5- to 10-fold faster rate of glutamine consumption than nonmalignant cells (16). When the body is under stress and experiencing high metabolic demands, the intracellular glutamine pool is approximately halved (17).

In a recent systematic review, Leung and Chan (18) reported that glutamine showed a statistically significant benefit with respect to reducing the risk and severity of radiation-induced oral mucositis compared with either placebo or no treatment. However, a multidisciplinary team of European head and neck cancer experts reached an opposite consensus on the prophylaxis and management of mucositis (19). Because of the wide range of findings in the literature, the panelists did not recommend glutamine as a preventative treatment for oral mucositis for head and neck cancer patients whether or not they were receiving chemotherapy.

Therefore, we conducted this Phase III RCT with the objective of evaluating whether oral glutamine decreased acute toxicities during RT. The primary and secondary endpoints were radiation-induced oral mucositis and neck dermatitis, respectively. We hypothesized that glutamine might play a role in easing RT-induced acute toxicity.

Methods

Participants, randomization, and interventions

This single-center, parallel, 2-armed RCT recruited 71 patients from February 2015 through August 2016 at a university hospital. We excluded patients with diabetes mellitus, renal or hepatic insufficiency, history of prior irradiation or sepsis, distant metastasis, or with an Eastern Cooperative Oncology Group (ECOG) performance status score of $\geq$2. The oral mucosa and the neck skin at baseline were healthy in all patients. We explained the study rationale to the trial participants and obtained written informed consent from them before enrollment. All the patients had histologic proof of cancer in the nasopharynx, oropharynx, hypopharynx, larynx, or oral cavity, and tumor stage was classified according to the seventh edition of the American Joint Committee on Cancer Cancer Staging Manual and Handbook (20).

A central randomization center used computer-generated tables to allocate intervention for 71 patients with stages I–IV head and neck cancers (allocation ratio 1:1). The patients were randomly assigned to receive oral L-glutamine (10 g L-glutamine and 5 g maltodextrin) or placebo (15 g maltodextrin) 3 times daily beginning 1 wk before RT, during RT, and for 2 wk after completion of RT. Both groups were instructed to orally consume either glutamine or placebo dissolved in cold water 30 min before a meal, 3 times per day. The patients were not allowed to consume any supplement containing L-glutamine (other than that prescribed by the investigators) during the intervention. Both glutamine and placebo could also be administered via a nasogastric feeding tube; all the packages for glutamine or placebo looked identical; and the glutamine and maltodextrin were both in the form of white powder. The patients, care providers, research coordinators, and study investigators were blinded to group assignment.

Ethics statement

The study protocols were approved by the Ethics and Research Committee of the university, and the trial was conducted under the compliance of the Institutional Review Board regulations in accordance with the Helsinki Declaration of 1975 as revised in 1983. The trial was registered at clinicaltrials.gov as NCT03015077.

All the patients provided written informed consent for treatment prior to randomization; patient information was anonymized and deidentified before analysis, so that all data were analyzed anonymously and prospectively. The placebo and glutamine supplements were manufactured by Sympt-X; this supplier had no decision-making role in the design or conduct of the study; collection, management, analysis, and interpretation of data; or in the preparation, review, approval, or submission of the manuscript.

Treatment

Each patient received a dental evaluation for oral hygiene prior to computed tomography simulation for intensity-modulated RT. All patients received intensity-modulated RT and the scheduled doses were given once per day, 5 d/wk. Postoperative patients received the planned course of adjuvant RT of 60–66 Gy in 2-Gy fractions to the post-operative high-risk region. The course of radiation was initiated $\leq$6 wk after the operation. The patients not receiving surgery received definitive treatment of 70 Gy in 2-Gy fractions. The target included the primary tumor and the lymph nodes involved. Any possible local subclinical infiltration was taken into consideration for the field design. The oral cavity was contoured in all cases for documentation of the oral cavity dose. In patients with oral cavity cancer, the oral cavity may overlap with the high dose area. Furthermore, computed tomography simulation with a new fixation was repeated if the mask did not fit and immobilization was poor. Adaptive RT plans were made according to our department’s protocol.

Forty-three patients received chemotherapy concurrently with RT. The chemotherapy regimen consisted of cisplatin or carboplatin with or without the addition of 5-fluorouracil, or paclitaxel. Seven patients in the placebo group and 7 in the glutamine group received 5-fluorouracil. Some patients had weekly chemotherapy whereas others had chemotherapy once every 3 wk. The choice of systemic therapy was individualized based on patient characteristics, transportation requirements, and in agreement with our institutional guidelines.

Upon signing for enrollment, all patients agreed to consume no nutritional supplement other than what the researchers provided. One patient violated this protocol and was excluded from the per-protocol (PP) analysis. Since this patient completed RT, he was included in the completers analysis. None of the patients had gastrostomy. One patient in the placebo group and 1 in the glutamine group had a nasogastric feeding tube inserted for better nutrition during the course of RT.

Data collection and assessment

Baseline characteristic data included patient age, gender, primary tumor location, cancer stage, ECOG performance status score, anthropometry, biochemical laboratory data, substance use such as alcohol, betel nut, or cigarette, BMI, prognostic nutritional index (PNI), and adjunct treatment details. We
measured triceps skin fold (TSF), mid-upper-arm circumference (MAC), and mid-upper-arm muscle circumference (MAMC) to evaluate body fat and muscle mass. The BMI is defined as the body weight divided by the square of the body height (kg/m²). We estimated the nutritional status from Niederman’s nutritional index as follows:

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PNI = 158 - 16.6 \times (\text{ALB}) - 0.78 \times (\text{TSF}) - 0.20 \times (\text{TFN}) - 5.8 \times (\text{LS})
\]

where ALB is the serum albumin level (g/dL), TSF is the triceps skin fold (mm), TFN is the serum transferrin level (mg/dL), and LS is the lymphocyte score. The LS is on a scale of 0–2, where 0 = total lymphocyte count <1000, 1 = total lymphocyte count of 1000–2000, and 2 = total lymphocyte count >2000.

The primary and secondary endpoints were radiation-induced oral mucositis and neck dermatitis, respectively. They were evaluated once a week during RT and 1 wk after RT using the National Cancer Institute Common Toxicity Criteria (CTCAE) version 4.03 (http://ctep.cancer.gov/reporting/ctc.html). The scoring was done as the patients proceeded through treatment: 1 project assistant took photographs of the oral cavity and the neck, and 2 different physicians reached agreement while scoring the same patient in each clinical visit. When the grades of mucositis varied from site to site in the oral cavity, the highest grade was recorded for the analysis, and the highest grade of dermatitis in the irradiated field was also recorded weekly. The skin care management strategy involved prescribing topical silver sulfadiazine cream (1%) for acute radiation dermatitis.

Completers’ analyses

Table 1 shows the characteristics of 64 patients included in the trial, who were aged 35–75 y (median: 51 y). The majority of patients (65.6%, N = 42) had oral cavity cancer. In Table 2, 67.2% (N = 43) of the patients suffered from Grades 2–4 oral mucositis. Of the patients with Grades 2–4 oral mucositis, 17 were in the glutamine arm and 26 in the placebo arm (OR: 0.33; 95% CI: 0.11, 0.98; P = 0.045). The mean dose to the oral cavity in the patients with Grades 0–1 mucositis and those with Grades 2–4 mucositis were 3416.6 ± 1319.6 cGy and 4610.6 ± 1317.6 cGy, respectively (OR: 1.07; 95% CI: 1.02, 1.12; P = 0.004). However, the maximum point dose to the oral cavity was not significantly different between Grades 0–1 and Grades 2–4 oral mucositis. For the patients with Grades 2–4 oral mucositis, the incidence of opioid use was significantly higher (OR: 9.02; 95% CI: 2.67, 30.45; P < 0.001). Although there was no significant influence from baseline BMI, the decrease of BMI during RT was associated with a higher severity of oral mucositis (OR: 0.32; 95% CI: 0.17, 0.61; P < 0.001). No significant differences in the baseline nutritional status, primary tumor location, severity of neck dermatitis, maximum dose to the oral cavity, RT interruption days, PNI change during RT, performance status, clinical stage, operation type, with or without chemotherapy, cigarette or alcohol consumption history, betel nut chewing habits, or pretreatment biochemical profile were observed (all P > 0.05).

In Table 3, the decrease of BMI strongly correlated with more severe oral mucositis (OR: 0.41; 95% CI: 0.20, 0.84; P = 0.015) in the multivariate completers’ analysis.

Per-protocol analyses

As shown in Supplemental Table 1, oral mucositis developed in all patients in the placebo arm and in 96.7% of patients in the glutamine arm. The mean maximum mucositis grade was 2.1 ± 0.8 and 1.6 ± 0.6 in the placebo and glutamine arms, respectively (P = 0.009). Supplemental Figure 1 shows the mean weekly CTCAE score, which grades the severity of oral mucositis in the 2 arms. In Supplemental Table 2, 59 patients (placebo, n = 29; glutamine, n = 30) were included. Although there was no significant influence of pre-RT BMI, the decrease in BMI during RT was associated with a higher severity of oral mucositis (OR: 0.32; 95% CI: 0.17, 0.61; P < 0.001). In Supplemental Table 3, the decrease in BMI strongly correlated with more severe oral mucositis (OR: 0.40; 95% CI: 0.20, 0.83; P = 0.014) in multivariate PP analysis.

Acute RT-induced dermatitis developed in all patients in both arms as shown in Supplemental Table 1. The mean maximum grade of dermatitis between the 2 arms showed no statistical difference (1.7 ± 0.6 compared with 1.5 ± 0.6, P = 0.221). Supplemental Figure 2 shows the mean weekly CTCAE score, which grades the severity of neck dermatitis in the 2 arms.

Discussion

In this double-blind RCT for patients with head and neck cancer undergoing RT, we evaluated the effectiveness of oral glutamine and found that it decreased the mean maximum severity of oral mucositis compared with placebo (1.6 ± 0.6
FIGURE 1  CONSORT diagram: study enrollment and randomization. CONSORT, Consolidated Standards of Reporting Trials.

compared with 2.1 ± 0.8, P = 0.009; Supplemental Table 1) in a PP analysis. This effect was not significant for completers (OR: 0.3; 95% CI: 0.05, 1.67; P = 0.169; Table 3) and in PP multivariate analysis (OR: 0.3; 95% CI: 0.05, 1.69; P = 0.172; Supplemental Table 3). Although the hypothesis was not confirmed, we found a significant association between the decrease in BMI and increased severity of oral mucositis.

The present study was unique in that our patients had various head and neck cancers, although the majority had oral cavity cancer (65.6%, N = 42). This may contribute to a higher incidence or severity of oral mucositis because the oral mucosa is in a high-dose area for these patients. Under such circumstances, we tested whether oral glutamine might help relieve the incidence and severity of oral mucositis with recorded toxicity up to 70 Gy. Oral glutamine was less severe in the glutamine arm (1.6 compared with 2.6, P = 0.0058). In our present study, such effect was not seen in the multivariate analysis.

Most recently, Tsujimoto et al. (25) reported that glutamine significantly decreased the severity of mucositis in the oral cavity, pharynx, and larynx induced by chemoradiation in patients with head and neck cancers. However, they did not include any patients with oral cavity cancer. In the present study, the dosage of glutamine was 30 g/d divided into 3 doses. A previous study that demonstrated positive effects in alleviation of oral mucositis used a dose range of 10–30 g/d (18).

One of our patients dropped out due to his concerns that glutamine might be utilized by the cancer cells. In fact, several research studies have demonstrated that glutamine is taken up preferentially by healthy tissues, such as the muscles, gut mucosa, and lymphocytes (16, 26–28). Cancer growth is reduced by glutamine in relation to the patients’ defenses and capability to tolerate chemotherapy (29).
### TABLE 1  Patient characteristics\(^1\)

|                         | Placebo group (n = 33) | Glutamine group (n = 31) | \(P\) value |
|-------------------------|------------------------|--------------------------|-------------|
| Gender                  | —                      | —                        | 0.347       |
| Male                    | 32 (97%)               | 27 (90.3%)               |             |
| Female                  | 1 (3%)                 | 3 (9.7%)                 |             |
| Age, y                  | 52.6 ± 10.3            | 52.2 ± 9.5               | 0.888       |
| Primary tumor location  | —                      | —                        | 0.693       |
| Nasopharynx             | 7 (21.2%)              | 9 (12.9%)                |             |
| Oropharynx              | 3 (9.1%)               | 4 (12.9%)                |             |
| Hypopharynx             | 2 (6.1%)               | 1 (3.2%)                 |             |
| Larynx                  | 0 (0%)                 | 1 (3.2%)                 |             |
| Oral cavity             | 21 (63.6%)             | 21 (67.7%)               |             |
| Stage                   | —                      | —                        | 0.708       |
| I                       | 2 (6.1%)               | 4 (12.9%)                |             |
| II                      | 5 (15.2%)              | 3 (9.7%)                 |             |
| III                     | 8 (24.2%)              | 6 (19.4%)                |             |
| IV                      | 18 (54.5%)             | 18 (58.1%)               |             |
| ECOG                    | —                      | —                        | 0.228       |
| 0                       | 5 (15.2%)              | 1 (3.2%)                 |             |
| 1                       | 27 (81.8%)             | 28 (90.3%)               |             |
| 2                       | 1 (3.0%)               | 2 (6.5%)                 |             |
| Operation               | —                      | —                        | 0.782       |
| Biopsy only             | 10 (30.3%)             | 10 (32.3%)               |             |
| Wide excision           | 1 (3.0%)               | 2 (6.5%)                 |             |
| Primary tumor excision with neck dissection | 22 (66.7%) | 19 (61.3%) |             |
| Total dose of irradiation, Gy | —                      | —                        | 0.777       |
| 60                      | 11 (33.3%)             | 13 (41.9%)               |             |
| 66                      | 11 (33.3%)             | 9 (29.0%)                |             |
| 70                      | 11 (33.3%)             | 9 (29.0%)                |             |
| Maximum dose to oral cavity, cGy | 6712.379 ± 560.4868   | 6254.010 ± 1531.4400     | 0.125       |
| Mean dose to oral cavity, cGy | 4459.727 ± 1172.7615   | 3962.439 ± 1631.9216     | 0.165       |
| Chemotherapy            | —                      | —                        | 0.557       |
| No                      | 8 (24.2%)              | 8 (25.8%)                |             |
| Yes                     | 25 (75.8%)             | 23 (74.2%)               |             |
| Hypertension            | —                      | —                        | 0.173       |
| No                      | 26 (78.8%)             | 19 (61.3%)               |             |
| Yes                     | 7 (21.2%)              | 12 (38.7%)               |             |
| Alcohol use             | —                      | —                        | 0.410       |
| No                      | 11 (33.3%)             | 7 (22.6%)                |             |
| Yes                     | 21 (66.7%)             | 24 (77.4%)               |             |
| Betel use               | —                      | —                        | 0.734       |
| No                      | 6 (18.2%)              | 4 (12.9%)                |             |
| Yes                     | 27 (81.8%)             | 27 (87.1%)               |             |
| Cigarette use           | —                      | —                        | 0.512       |
| No                      | 7 (21.2%)              | 4 (12.9%)                |             |
| Yes                     | 26 (78.8%)             | 27 (87.1%)               |             |
| BMI, kg/m²              | 23.30 ± 4.26           | 23.33 ± 4.15             | 0.973       |
| Recommended daily intake of calories, kcal/d | 2227.76 ± 331.91 | 2272.68 ± 378.42 | 0.624       |
| Estimated daily intake of calories, kcal/d | 1457.96 ± 352.32 | 1423.79 ± 388.91 | 0.714       |
| Tumor classification    | —                      | —                        | 0.471       |
| 0                       | 1 (3.0%)               | 0 (0%)                   |             |
| 1                       | 8 (24.2%)              | 8 (29.0%)                |             |
| 2                       | 9 (27.3%)              | 13 (41.9%)               |             |
| 3                       | 5 (15.2%)              | 2 (6.5%)                 |             |
| 4                       | 10 (30.3%)             | 7 (22.6%)                |             |
| Nodal classification    | —                      | —                        | 0.898       |
| 0                       | 10 (32.3%)             | 10 (32.3%)               |             |
| 1                       | 8 (24.2%)              | 6 (19.4%)                |             |
| 2                       | 13 (39.4%)             | 14 (45.2%)               |             |
| 3                       | 2 (6.1%)               | 1 (3.2%)                 |             |
| Opioid use              | —                      | —                        | 0.076       |
| Yes                     | 10(30.3%)              | 17 (54.8%)               |             |
| No                      | 23 (69.7%)             | 14 (45.2%)               |             |
| RT interruption, d      | —                      | —                        | 0.983       |
|                         | 1.6 ± 2.943            | 1.58 ± 3.897             |             |

\(^1\)Independent \(t\) test and chi-square analysis. Values are \(N\) (%) or mean ± SD. ECOG, Eastern Cooperative Oncology Group performance status score; RT, radiotherapy.
| Variable                                           | Mucositis (0–1) control | Mucositis (2–4) case | OR (95% CI) | P value |
|----------------------------------------------------|-------------------------|----------------------|-------------|---------|
| **Group**                                          |                         |                      |             |         |
| Glutamine                                          | 14 (66.7%)              | 17 (39.5%)          | 0.33 (0.11, 0.98) | 0.045   |
| Placebo                                            | 7 (33.3%)               | 26 (60.5%)          | 1.00        |         |
| **Gender**                                         |                         |                      |             |         |
| Male                                               | 20 (95.2%)              | 40 (93.0%)          | 0.67 (0.07, 6.83) | 0.733   |
| Female                                             | 1 (4.8%)                | 3 (7.0%)            | 1.00        |         |
| **Age, y**                                         | 52.3 ± 11.4             | 52.4 ± 9.1          | 1.00        | 0.967   |
| **Primary tumor site**                             |                         |                      |             |         |
| Oral cavity cancer                                 | 11 (52.4%)              | 31 (72.1%)          | 2.35 (0.79, 6.95) | 0.123   |
| Others                                             | 10 (47.6%)              | 12 (27.9%)          | 1.00        |         |
| **Stage**                                          |                         |                      |             |         |
| I                                                  | 3 (14.3%)               | 3 (7%)              | 1.00        |         |
| II                                                 | 2 (9.5%)                | 6 (14%)             | 3.00 (0.31, 28.83) | 0.342   |
| III                                                | 4 (19.1%)               | 10 (23.2%)          | 2.50 (0.35, 18.04) | 0.364   |
| IV                                                 | 12 (57.1%)              | 24 (55.8%)          | 2.00 (0.35, 11.44) | 0.436   |
| **T classification**                               |                         |                      |             |         |
| 0–2                                                | 13 (61.9%)              | 27 (62.8%)          | 1.00        |         |
| 3–4                                                | 8 (38.1%)               | 16 (37.2%)          | 0.96 (0.33, 2.82) | 0.945   |
| **N classification**                               |                         |                      |             |         |
| 0–1                                                | 10 (47.6%)              | 24 (55.8%)          | 1.00        |         |
| 2–3                                                | 11 (52.4%)              | 19 (44.2%)          | 0.72 (0.25, 2.05) | 0.538   |
| **ECOG**                                           |                         |                      |             |         |
| 0                                                  | 2 (9.5%)                | 4 (9.3%)            | 1.00        |         |
| 1                                                  | 17 (81.0%)              | 38 (88.4%)          | 1.12 (0.19, 6.70) | 0.903   |
| 2                                                  | 2 (9.5%)                | 1 (2.3%)            | 0.25 (0.01, 4.73) | 0.355   |
| **Operation**                                      |                         |                      |             |         |
| Biopsy only                                        | 6 (30.0%)               | 12 (30.8%)          | 1.00        |         |
| Wide excision                                      | 1 (5.0%)                | 2 (5.1%)            | 1.00 (0.08, 13.37) | 0.999   |
| Primary tumor excision with neck dissection        | 13 (65.0%)              | 25 (64.1%)          | 0.96 (0.29, 3.15) | 0.949   |
| **Maximum dose to oral cavity, cGy**               | 6146.9 ± 1251.4         | 6658.1 ± 1077.5     | 1.04 (0.99, 1.10) | 0.139   |
| **Mean dose to oral cavity, cGy**                  | 3416.6 ± 1319.6         | 4610.6 ± 1317.6     | 1.07 (1.02, 1.12) | 0.004   |
| **Chemotherapy**                                   |                         |                      |             |         |
| Yes                                                | 14 (66.7%)              | 34 (79.1%)          | 1.89 (0.59, 6.07) | 0.286   |
| No                                                 | 7 (33.3%)               | 9 (20.9%)           | 1.00        |         |
| **Drinking history**                               |                         |                      |             |         |
| Yes                                                | 15 (71.4%)              | 31 (72.1%)          | 1.03 (0.33, 3.29) | 0.956   |
| No                                                 | 6 (28.6%)               | 12 (27.9%)          | 1.00        |         |
| **Betel nut use history**                          |                         |                      |             |         |
| Yes                                                | 17 (81.0%)              | 37 (86.0%)          | 1.45 (0.36, 5.82) | 0.600   |
| No                                                 | 4 (19.0%)               | 6 (14.0%)           | 1.00        |         |
| **Smoking history**                                |                         |                      |             |         |
| Yes                                                | 15 (71.4%)              | 38 (88.4%)          | 3.04 (0.81, 11.48) | 0.101   |
| No                                                 | 6 (28.6%)               | 5 (11.6%)           | 1.00        |         |
| **Incidence of opioid use**                        |                         |                      |             |         |
| Yes                                                | 5 (23.8%)               | 31 (73.8%)          | 9.02 (2.67, 30.45) | <0.001  |
| No                                                 | 16 (76.2%)              | 11 (26.2%)          | 1.00        |         |
| **RT interruption, d**                             | 0.3 ± 0.8               | 2.2 ± 4.0           | 1.57 (0.93, 2.64) | 0.091   |
| **Dermatitis grading**                             |                         |                      |             |         |
| 0–1                                                | 13 (61.9%)              | 17 (39.5%)          | 1.00        |         |
| 2–3                                                | 8 (38.1%)               | 26 (60.5%)          | 2.49 (0.85, 7.26) | 0.096   |
| **BMI change during RT (post-RT data minus pre-RT data), kg/m²** | 0.3 ± 1.6              | −1.7 ± 1.5          | 0.32 (0.17, 0.61) | <0.001  |
| **Pre-RT BMI, kg/m²**                              | 23.1 ± 4.3              | 23.4 ± 4.2          | 1.02 (0.90, 1.16) | 0.773   |
| **Post-RT BMI, kg/m²**                             | 22.8 ± 4.3              | 21.7 ± 4.0          | 0.93 (0.82, 1.07) | 0.313   |
| **Albumin level change (post-RT minus pre-RT), g/dL** | 0.006 ± 0.33            | 0.056 ± 0.29        | 1.74 (0.29, 10.53) | 0.547   |
| **PNI change (post-RT minus pre-RT)**              | 5.1 ± 12.1              | 6.3 ± 11.1          | 1.01 (0.96, 1.06) | 0.685   |
| **TSF, mm**                                        | 9.4 ± 7.5               | 9.7 ± 8.4           | 1.04 (0.91, 1.18) | 0.595   |
| **MAC, cm**                                        | 27.0 ± 3.5              | 27.2 ± 2.7          | 1.02 (0.85, 1.22) | 0.825   |
| **PNI, %**                                         | 17.6 ± 12.1             | 22.9 ± 13.8         | 1.03 (0.99, 1.08) | 0.145   |
| **Creatinine, mg/dL**                              | 0.96 ± 0.30             | 0.90 ± 0.21         | 0.36 (0.04, 3.06) | 0.346   |
Imai et al. (30) designed a Phase II RCT of 40 patients to evaluate the preventive effect of an oral nutrition supplement composed of β-hydroxy-β-methylbutyrate, arginine, and glutamine on RT-induced dermatitis in patients with head and neck cancers. They found that the incidence of Grade ≥3 dermatitis did not differ between the 2 groups, although the incidence of Grade ≥2 dermatitis was lower, and the duration of Grade ≥1 and Grade ≥2 dermatitis was shorter in patients who took the supplement. The present study used glutamine alone, and the radiodermatitis between the two arms showed no statistical difference.

Some authors reported that Grade ≥3 RT-induced oral mucositis would aggravate malnutrition during RT (31). Another team stated that pretreatment low BMI might be a risk factor of moderate to severe oral mucositis compared with patients with normal BMI (≥22.0 kg/m²) (OR: 9.07; 95% CI: 1.72, 47.68; P < 0.01) (32). The baseline BMI in our patients was normal according to the WHO classification. To the best of our knowledge, the present study is the first one to confirm a strong connection between oral mucositis and change in BMI in head and neck cancer patients undergoing RT by multivariable logistic regression. After adjusting for baseline nutritional status and biochemical profile, primary tumor location and stage, severity of neck dermatitis, mean and maximum dose to the oral cavity, RT interruption days, PNI change during RT, performance status, operation, chemotherapy, alcohol or tobacco use history, betel nut chewing habits, incidence of opioid use, etc., the change in BMI during RT was still an independent and stable factor in the severity of oral mucositis.

We postulate that a reciprocal causation occurs between the decreased BMI and the severity of oral mucositis. When more severe mucositis causes an inability to eat, inadequate oral intake decreases the body weight and hence the BMI. Debilitated nutritional status from weight loss reduces the healing capability, and therefore leads to more severe mucositis. Under these circumstances, an oral nutritional supplement such as glutamine alone may not reverse the condition. The internal mechanism

| Variable | Mucositis (0–1) control | Mucositis (2–4) case | OR (95% CI) | P value |
|----------|-------------------------|----------------------|-------------|---------|
| GOT, U/l | 25.0 ± 5.5              | 29.8 ± 13.1          | 1.05 (0.99, 1.12) | 0.125   |
| GPT, U/l | 26.7 ± 11.8             | 30.5 ± 20.2          | 1.02 (0.99, 1.06) | 0.235   |
| Albumin, g/dL | 4.4 ± 0.3   | 4.2 ± 0.4            | 0.17 (0.03, 1.02) | 0.052   |
| Total protein, g/dL | 7.5 ± 0.4   | 7.3 ± 0.5            | 0.83 (0.27, 2.56) | 0.748   |
| CRP, mg/dL | 4.1 ± 4.2    | 7.1 ± 12.8           | 1.04 (0.96, 1.11) | 0.345   |
| Transferrin, mg/dL | 251.6 ± 47.5 | 239.8 ± 39.6        | 0.99 (0.98, 1.01) | 0.294   |
| WBC count, × 10⁹/mm³ | 7.3 ± 3.0    | 7.0 ± 2.3            | 0.96 (0.79, 1.18) | 0.726   |
| Total lymphocyte count, × 10⁹/mm³ | 27.5 ± 9.6   | 28.3 ± 7.3           | 1.01 (0.95, 1.08) | 0.677   |
| RBC count, × 10¹²/mm³ | 4.4 ± 0.8    | 4.4 ± 0.7            | 0.98 (0.49, 1.95) | 0.952   |
| Hemoglobin, g/dL | 12.7 ± 1.9    | 13.0 ± 1.7           | 1.11 (0.82, 1.50) | 0.490   |
| Hematocrit, % | 39.0 ± 5.4    | 39.5 ± 5.1           | 1.02 (0.92, 1.13) | 0.739   |
| BUN, mg/dL | 15.5 ± 7.5    | 14.1 ± 6.1           | 0.97 (0.90, 1.05) | 0.412   |

1Multiple logistic regressions. Values are N (%) or mean ± SD. BUN, blood urea nitrogen; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group performance status score; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; MAC, mid-upper-arm muscle circumference; MAMC, mid-upper-arm muscle circumference; PNI, prognostic nutritional index (PNI (%) = 158 – 16.6 × (albumin) – 0.78 × (triceps skin fold thickness) – 0.2 × (serum transferrin) – 5.8 × (lymphocyte score, total lymphocyte count <1000: score 0; total lymphocyte count 1000–2000: score 1; total lymphocyte count >2000: score 2)); RBC, red blood cell; RT, radiotherapy; TSF, triceps skin fold thickness; WBC, white blood cell.

| Variable          | OR (95% CI) | P value |
|-------------------|-------------|---------|
| Glutamine         | 0.32 (0.06, 1.62) | 0.167   |
|                   | 0.30 (0.05, 1.67) | 0.169   |
|                   | 0.44 (0.12, 1.60) | 0.212   |
| Placebo           | 1.00        |         |
|                   | 1.00        |         |
|                   | 1.00        |         |
| Mean dose to oral cavity (per Gy) | 1.04 (0.97, 1.11) | 0.296   |
|                   | 1.02 (0.96, 1.09) | 0.484   |
|                   | 1.05 (0.99, 1.11) | 0.089   |
| Incidence opioid use | 3.90 (0.73, 20.77) | 0.111   |
|                  | 4.93 (0.79, 30.73) | 0.088   |
|                  | 5.29 (1.38, 20.25) | 0.015   |
|                  | —           |         |
|                  | 0.43 (0.22, 0.85) | 0.015   |
|                  | 0.41 (0.20, 0.84) | 0.015   |
|                  | 0.05        |         |
|                  | 0.00        |         |
|                  | 1.00        |         |
| BMI change (post-RT minus pre-RT), kg/m² | 1.51 (0.06, 35.99) | 0.799   |
|                  | 0.20 (0.01, 3.98) | 0.288   |
|                  | 1.00        |         |
|                  | 0.95 (0.86, 1.04) | 0.241   |
|                  | 1.01 (0.95, 1.07) | 0.839   |

1Multiple logistic regressions. RT, radiotherapy.
of this reciprocal causation is not clear and further laboratory exploration is warranted.

A limitation of the present study is that 3 out of the 6 patients (50%) in the placebo arm discontinued taking placebo because of an aversion to the taste of maltodextrin. An improved design with a different placebo is required in the future. In addition, 7 subjects did not complete RT. Presumably, they might not have developed the mucositis condition that our intervention was designed to treat. Dropping those subjects might have affected the randomization of the study. In addition, CTCAE version 4.03 is a clinician assessment of clinical symptoms rather than either patient-reported outcomes or an objective physician score of mucosal appearance (33). Perhaps the 25% decrease in certain grades of mucositis was overambitious and the study was consequently underpowered. The duration of Grade 3 mucositis and patient-reported severity should be taken into consideration in future study design (34). Finally, the present study was conducted in a single cancer center, so multi-institutional validation is needed.

Our data were collected prospectively, eliminating potential recall bias and allowing standardized toxicity scoring. The decrease in BMI during RT is a simple index for the severity of oral mucositis. This has implications for patient counseling and clinical management. Further investigation with larger sample numbers into weight maintenance during RT and acute toxicity is warranted. To date, the oral form of glutamine appears to be well tolerated, although the duration of the clinical follow-up has not been long. Close follow-up of the patients in this trial will be maintained to determine long-term clinical outcomes.

In conclusion, despite several positive results from the literature, oral glutamine failed to reduce RT-induced oral mucositis or neck dermatitis in patients with head and neck cancer. However, the decrease in BMI strongly correlated with a higher severity of oral mucositis during RT. The present RCT corroborates this effect.

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References

1. Cerchietti LC, Navigante AH, Lutteral MA, Castro MA, Kirchuk R, Bonomi M, Cabalar ME, Roth B, Negrette G, Sheinker B, et al. Double-blinded, placebo-controlled trial on intravenous L-alanyl-L-glutamine in the incidence of oral mucositis following chemoradiotherapy in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys 2006;65(5):1330–7.

2. Bockel S, Vaillard A, Levy A, Francois S, Bourdis M, Le Gallic C, Riccobono D, Amnedde P, Drouet M, Tao Y, et al. Pharmacological modulation of radiation-induced oral mucosal complications. Cancer Radiother 2018;22(5):429–37.

3. Saadeh CE. Chemotherapy- and radiotherapy-induced oral mucositis: review of preventive strategies and treatment. Pharmacotherapy 2005;25(4):540–54.

4. Vera-Llonch M, Oster G, Hagiwara M, Sonis S. Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma. Cancer 2006;106(2):329–36.

5. Sonis ST. Oral mucositis. Anti-Cancer Drugs 2011;22(7):607–12.

6. Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys 2007;68(4):1110–20.

7. Trotti A, Bellin LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, Komaroff E, Nalsyank L, Zilberberg MD. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003;66(3):253–62.

8. Nonzee NJ, Dandade NA, Patel U, Markossian T, Aguilnik M, Arghiris A, Patel JD, Kern RC, Munchi HG, Calhoun EA, et al. Evaluating the supportive care costs of severe radiochemotherapy-induced mucositis and pharyngitis: results from a Northwestern University Costs of Cancer Program pilot study with head and neck and nonsmall cell lung cancer patients who received care at a county hospital, a Veterans Administration hospital, or a comprehensive cancer care center. Cancer 2008;113(6):1446–52.

9. Rubenstein EB, Peterson DE, Schubert M, Keefe D, McGuire D, Epstein J, Elting LS, Fox PC, Cooksley C, Sonis ST. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004;100(9 Suppl):2026–46.

10. Gibson RJ, Keefe DM, Lalla RV, Bateman E, Blilevients N, Fijstra M, King EE, Stringer AM, van der Velden WI, Yazbeck R, et al. Systematic review of agents for the management of gastrointestinal mucositis in cancer patients. Support Care Cancer 2013;21(1):313–26.

11. Worthington HV, Clarkson JE, Eden OB. Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev 2007(4):CD000978. DOI: 10.1002/14651858.CD000978.pub3.

12. Stokman MA, Spijkervet FK, Boezen HM, Schouten JP, Roedenburg JL, de Vries EG. Preventive intervention possibilities in radiotherapy- and chemotherapy-induced oral mucositis: results of meta-analyses. J Dent Res 2006;85(8):690–700.

13. Mims J, Bansal N, Bharadwaj MS, Chen X, Molina AJ, Tsang AW, Furdai CM. Energy metabolism in a matched model of radiation resistance for head and neck squamous cell cancer. Radiat Res 2015;183(3):291–304.

14. Papanikolopoulou A, Syrigos KN, Drakoulis N. The role of glutamine supplementation in thoracic and upper aerodigestive malignancies. Nutr Cancer 2015;67(2):231–7.

15. Watford M. Glutamine metabolism and function in relation to proline synthesis and the safety of glutamine and proline supplementation. J Nutr 2008;138(10):2003–7.

16. Souba WW. Glutamine and cancer. Ann Surg 1993;218(6):715–28.

17. Furst P, Albers S, Stehle P. Evidence for a nutritional need for glutamine in catabolic patients. Kidney Int 1989;27:S287–92.

18. Leung HW, Chan AL. Glutamine in alleviation of radiation-induced severe oral mucositis: a meta-analysis. Nutr Cancer 2016;68(5):734–42.

19. De Sanctis V, Bossi P, Sanguineti G, Trippa F, Ferrari D, Bacigalupo A, Ripamonti CI, Buglione M, Pergolizzi S, Langendijk JA, et al. Mucositis in head and neck cancer patients treated with radiotherapy and systemic therapies: literature review and consensus statements. Crit Rev Oncol Hematol 2016;100:147–66.

20. Edge SB, Compton NC. The American Joint Committee on Cancer; the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17(6):1471–4.

21. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Oral and gastrointestinal mucositis. Cancer 2004;100(9 Suppl):2026–46.

22. Niederman MS, Merrill WW, Ferranti RD, Pagano KM, Palmer LB, Reynolds HY. Nutritional status and bacterial binding in the lower respiratory tract in patients with chronic tracheostomy. Ann Int Med 1984;100(6):795–800.

23. Vidal-Casariego A, Calleja-Fernandez A, Ballesteros-Pomar MD, We thank Chiung-Yun Chang, Alexander Gittin, Jin-Mei Pan, and the Division of Medical Statistics and Bioinformatics, Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung Medical University for their help. The authors’ contributions were as follows—HHL and CIH: original idea, analysis, and composition of the manuscript; YTW, KHL, and HYC: interpretation of data and statistical analysis; MYH, CMH, CHC, FC, and PTF: acquisition of data, treatment of patients, and scoring of the toxicity by protocol; SSY and YYW: study design and clinical and technical support; and all authors: read and approved the final manuscript. None of the author declare any conflicts of interest.

References
mucositis and acute radiation-induced esophagitis: a retrospective study. Nutr Cancer 2013;65(3):424–9.

24. Huang EY, Leung SW, Wang CJ, Chen HC, Sun LM, Fang FM, Yeh SA, Hsu HC, Hsiung CY. Oral glutamine to alleviate radiation-induced oral mucositis: a pilot randomized trial. Int J Radiat Oncol Biol, Phys 2000;46(3):535–9.

25. Tsujimoto T, Yamamoto Y, Wasa M, Takenaka Y, Nakahara S, Takagi T, Tsugane M, Hayashi N, Maeda K, Inohara H, et al. L-Glutamine decreases the severity of mucositis induced by chemoradiotherapy in patients with locally advanced head and neck cancer: a double-blind, randomized, placebo-controlled trial. Oncol Rep 2015;33(1):33–9.

26. Savarese DM, Savy G, Vahdat L, Wischmeyer PE, Corey B. Prevention of chemotherapy and radiation toxicity with glutamine. Cancer Treat Rev 2003;29(6):501–13.

27. Kubota A, Meguid MM, Hitch DC. Amino acid profiles correlate diagnostically with organ site in three kinds of malignant tumors. Cancer 1992;69(9):2343–8.

28. Yoshida S, Kaibara A, Ishibashi N, Shirouzu K. Glutamine supplementation in cancer patients. Nutrition 2001;17(9):766–8.

29. Noe JE. L-glutamine use in the treatment and prevention of mucositis and cachexia: a naturopathic perspective. Integr Cancer Ther 2009;8(4):409–15.

30. Imai T, Matsuura K, Asada Y, Sagai S, Katagiri K, Ishida E, Saito D, Sadayasu R, Wada H, Saito S. Effect of HMB/Arg/Gln on the prevention of radiation dermatitis in head and neck cancer patients treated with concurrent chemoradiotherapy. Jpn J Clin Oncol 2014;44(5):422–7.

31. Jin T, Li KK, Li PJ, Huang S, Chen XZ, Chen M, Hu QY, Shi L, Chen YY. An evaluation of nutrition intervention during radiation therapy in patients with locoregionally advanced nasopharyngeal carcinoma. Oncotarget 2017;8(48):83723–33.

32. Saito N, Imai Y, Muto T, Sairenchi T. Low body mass index as a risk factor of moderate to severe oral mucositis in oral cancer patients with radiotherapy. Support Care Cancer 2012;20(12):3373–7.

33. Cristaudo A, Hickman M, Fong C, Sanghera P, Hartley A. Assessing novel drugs and radiation technology in the chemoradiation of oropharyngeal cancer. Medicines (Basel) 2018;5(3), 65, DOI:10.3390/medicines5030065.

34. Henke M, Alfonsi M, Foa P, Giralt I, Bardet E, Cerezo L, Salzwimmer M, Lizambri R, Emmerson L, Chen MG, et al. Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: a randomized, placebo-controlled trial. J Clin Oncol. 2011;29(20):2815–20.