RESEARCH ARTICLE

Oral Glutamine Supplementation Reduces Radiotherapy-induced Esophagitis in Lung Cancer Patients

Kanyilmaz Gul[1]*, Akmansu Muge[2], Atasever Taner[3], Elbag Sehri[4]

Abstract

Background: The purpose of this study was to assess the the efficacy of oral glutamine (GLN) in prevention of acute radiation-induced esophagitis in patients with lung cancer and determine the predictive role of clinical and dosimetric parameters. Materials and Methods: Thirty-two patients diagnosed with lung cancer were studied prospectively. Sixteen patients (50%) received prophylactic powdered GLN orally in doses of 10g/8h. Patients were treated 2 Gy per fraction daily, 5 days a week. We evaluated the grading of esophagitis daily at the end of each fraction of each treatment day until a cumulative dose of 50 Gy was reached. The primary end point was radiation-induced esophagitis. Results: All patients tolerated GLN well. Toxicity grade, weight loss, serum cytokine levels and esophageal transit times exhibited statistically significant improvement in the GLN receiving group. GLN suppressed the inflammation related to the disease and treatment and reduced toxicity with statistical significance. Conclusions: This study suggests a benefical role of oral GLN use in prevention and/or delay of radiation-induced esophagitis, in terms of esophageal transit time and serum immunological parameters, as well as weight loss.

Keywords: Radiotherapy - radiation esophagitis - glutamine - lung cancer

Asian Pac J Cancer Prev, **16 (1)**, 53-58

Introduction

Radiation therapy (RT) plays an important role in the treatment of locally advanced lung cancer, either postoperatively or definitively (Bradley, 2005). Acute esophagitis is a very common complication of RT in thoracic malignancies and may cause dose-limiting toxicity that is reported in 5-100% of patients treated with toracic radiotherapy (Belderbos et al., 2005). The main clinical signs of acute radiation esophagitis are dysphagia and odynophagia. The presence of these symptoms, which are clinical manifestations of dyskinesia and mucositis respectively, suggests that radiation induced acute esophagitis might be associated with altered organ motillity (Sasso et al., 2008). A variety of studies have shown that irradiation of the esophagus causes early mucosal changes and acute effects on esophageal motility or transit (Turkolmez et al., 2005; Sasso et al., 2008). Clinical and dosimetric factors may be related to the incidence and severity of acute radiation esophagitis. These factors are: age (Ahn et al., 2005) tumor stage (Choy et al., 1998) , nodal stage (Belderbos et al., 2005), concurrent chemoirradiation (Choy et al., 1998), mean esophageal dose and maximal dose point (Etiz et al., 2013), esophageal volume receiving >35 Gy (V35), V40, V45, V50,V60 (Topkan et al., 2009; Etiz et al., 2013) and percent length of esophagus in treatment volume.

After the administration of RT, inflammatory cytokines are released from the epithelium and the adjacent connective tissue. These cytokines include tumor necrosis factor-α (TNF-α), interleukin-1, interleukin-6 and also interleukin-8 (Shih et al., 2003).

Glutamine (GLN) is a neutral amino acid that acts as a substrate for nucleotide synthesis in most dividing cells such as enterocytes, lymphocytes, and fibroblasts as nitrogen source and/or alternative energy fuel. It is hypothesized that increased GLN demands of host, increase the capacity of endogenous production resulting in a strong GLN deprivation with detrimental effects on organ functions in cancer patients. In long term periods of cancer cachexia, an adequate nutrition support including GLN can essentially contribute to cover GLN needs and, thus to spare energy reserves of the host and to retard severe complications such as multi-organ failure. Due to the early *in vitro* knowledge that cancer cells preferably consume GLN, oncologists often refuse to supply GLN to the tumor-bearing host to avoid any potential risk (Kuhn et al., 2009). The experimental animal studies showed that, GLN supplements may be useful because they improve immunity. Subsequently, many human studies showed that the use of supplemental GLN resulted in beneficial effects on nitrogen metabolism, immunologic parameters and

*Department of Radiation Oncology, Faculty of Medicine, [1]Necmettin Erbakan University, Konya, [2]Gazi University, [3]Department of Nuclear Medicine, Medipol Hospital, [4]Department of Pathology, Faculty of Medicine, Gazi University, Ankara, Turkey *For correspondence: drgulgun@yahoo.com*

some nutritional indicators (Lacely et al., 1990). Huang et al. showed that GLN supplementation can decrease RT induced esophagitis in patients with head and neck neoplasia (Huang et al., 2000).

Release of chemicals by tumor, or the host immune system, may induce anorexia. Many proinflammatory cytokines have an effect on appetite, icluding IL-1α, IL-1β, and IL-6, IL-8, as well as TNF-α (Plata-Salaman et al., 1998). TNF-α, IL-1, and IL-6 play a role in muscle loss in cancer cachexia. Theoretically; support of cancer patients with involuntary weight loss and cachexia can be provided by the use of anti-inflammatory products.

The purpose of this study was to assess the the efficacy of oral GLN in prevention of acute radiation-induced esophagitis in patients with lung cancer and to determine the predictive role of clinical (such as, serum immunological parameters and esophageal transit time) and dosimetric paramete.

Materials and Methods

Patients

From January 2010 to August 2010, all patients diagnosed with lung cancer and eligible for definitive chemoradiotherapy were enrolled in this prospective study. The study was conducted according to the ethical principles laid down in the latest version of the Helsinki Declaration. Informed consent was obtained from all patients. The total number of patients was 32. Trial was stoped because of the changing the workplace and also results are presented late due to social reasons. All patients had the following inclusion criteria: histopathologic proof of lung cancer, indication for definitive radiotherapy, age ≥18 and <80, Karnofsky Performance Status (KPS) ≥70, no prior history of thoracic RT, no pretreatment dysphagia or ingestion difficulties, not having received any other supplementary products, no known GLN allergy.

Glutamine supplementation

GLN powder is one of the dietary supplements recommended to our patients. Sixteen patients in this study received prophylactic GLN powder (GLN Resource R, Nestle) at a dose of 30g/day (10g/8h orally, dissolved in water or fruit juices) starting one week before thoracic RT and continuing for two weeks after completion of RT. Although we planned to use glutamine in the entire study population,16 patients did not receive any supplementary products due to economical reasons or patients' self-choise.

Treatment

In this study we assessed the efficacy of oral GLN in prevention of acute radiation-induced esophagitis in patients with lung cancer and determine the predictive role of clinical (eg., serum immunological parameters and esophageal transit time) and dosimetric parameters.

Computerized tomography (CT)- based treatment planning is the standard routine in our Department in treating such patients. Contouring of target volumes and normal organs (esophagus, spinal cord, and lung) was carried out on each slice. The treatment planning for eligible patients was based on gross tumor volume (GTV) which contained both the primary tumor and involved lymp nodes. Clinical target volumes (CTV) were defined by adding a 1 cm margin to GTVs. Planning target volume (PTV)1 was defined by adding a 1cm margin to CTV and PTV2 was defined by adding a 1cm margin to GTV. Prescribed doses were 50 Gy to PTV1, and 60-66 Gy to PTV2. All patients received RT for 5 days a week, 2 Gy per fraction. The reason to stopted the administration at 50 Gy was due to the fact that the study included patients with small-cell carsinoma which are delivired total 50 Gy. Patients received chemotherapy according to their stage and perfomance status. Acute esophageal toxicity was graded by Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer criteria.

No anti-inflammatory drugs were administered to patients in order not affect the results of evaluation. In order to evaluate the immunological parameters of patients on the first and fifth weeks of treatment, blood was collected. IL-1 beta, IL-6, IL-8, TNF-alpha parameters were examined by the "enzyme-linked immunosorbent assay" (ELISA) kits (ELISA kits were supported by Nestle Company). Esophageal transit time was assessed by esophageal scintigraphy. After determination of baseline pre-treatment esophageal transit time, on the fifth week of treatment transit times were measured again.

Statistical methods

For the statistical analysis, the baseline demographic characteristics and patients were stratified according to whether GLN used. The following parameters were analyzed for correlation of acute esophagitis: age, gender, tumor stage, nodal stage, chemotherapy status, irradiated esophagus length, V5- V50 of esophagus. The rate of development of esophagitis with regard to primary parameter between treatment groups were evaluated using the chi-square test. In terms of other variables, the values obtained before treatment and during treatment, depending on the type of data were compared with the appropriate parametric or non-parametric tests. Frequency distributions were used to describe the categoric variables, whereas for the quantitative variables, mean, median, and ranges were used. Frequency distributions were compared by using either Chi-square test, Student's t-test, Pearson's exact test or Spearman's correlations. A p- value <0.05 was considered significant.

Results

There was no significant difference between GLN-supplemented and non-supplemented patients in terms of dosimetric parameters such as the mean esophageal dose, maximum esophageal point dose, irradiated esophagus length and volume, ratio of the irradiated length to total length of the esophagus in the field of treatment and ratio of the irradiated volume of esophagus to total volume of esophagus. In addition, the two groups were compared in terms of V5-V50. All values were seen to be higher in the group receiving GLN; V15, V20, V25 and V50 values demonstrated statistically significant elevation in

GLN-supplemented group.

A strong correlation between increasing age and esophagitis was found between each of the two sub-groups, i.e. both the GLN-supplemented and non-supplemented patients as well as in the grand total of all patients, but the results were not statistically significant. There was no significant correlation between esophagitis and T and N status and stage in the grand total of the patients. In the group which received GLN, none of these parameters correlated significantly with esophagitis, while T stage showed a statistically significant correlation to acute esophagitis in the group of patients which did not -receive GLN (p=0.03).

In GLN-supplemented patients treated with chemoradiotherapy, esophagitis was seen in 53.8% of patients (7 patients) whereas, in GLN-non-supplemented group, incidence of esophagitis was 100% with chemoradiotherapy. The p value for esophagitis incidence in all patients who did not receive GLN when treated by chemoradiotherapy was p=0.051.

When all of our patients were taken into consideration, we did not find a relation between esophagitis and ratio of length of the esophagus in the field of treatment versus total esophageal length. There also was not any correlation between esophagitis and ratio of irradiated esophageal segment versus total volume of the esophagus. However, in GLN-supplemented group, ratio of the treated portion of the esophagus versus total length of the esophagus is strongly related with esophagitis (p=0.041) whereas, there was no significant relation between these parameters in GLN-non-supplemented group. This can be interpreted as follows: this group of patients already developed esophagitis, regardless of irradiated length of the esophagus. Also, in GLN-supplemented group, esophagitis was correlated to ratio of esophageal volume in the treatment field versus total volume of esophagus. This relation was close to statistical significance (p=0.055).

In the grand total of our total patients, we did not find a relation between esophagitis and dosimetric parameters such as the mean esophageal dose, maximum esophageal point dose, irradiated esophagus length and volume and esophageal V5-50 parameters. However, in GLN-non-supplemented group, there was a relation close to statistical significance (p=0.053) between esophagitis and maximum esophageal point doses.Additionally V20,V25,V30,V35,V40 and V45 parameters had statistically significant association with osephagitis in GLN-non-supplemented group (respectively; p=0.042, p=0.042, p=0.042, p=0.033, p=0.033, p=0.033).

Esophageal scintigraphy was performed before and on the fifth week of RT to evaluate esophageal motility. Measurements were examined in three parts according to the anatomic structure of the esophagus. These are; the transit time of upper part of esophagus (1/3 ETT), the transit time of middle part of esophagus (2/3 ETT), the transit time of lower part of esophagus (3/3 ETT). Total esophageal transit time was also (ETT) calculated. In analyses of subgroups, ETT was statistically significantly prolonged in GLN-non-supplemented group. There were no differrences in both groups before treatment but at the end of treatment ETT was significantly prolonged in GLN-non-supplemented group (Table 1).

Patients were compared according to changes in cytokine levels at the beginning and at the end of treatment. In order to evaluate the immunological parameters (TNF-alpha, IL-1beta, IL-6 and IL-8 levels were evaluated) of patients on the first and fifth weeks of treatment, blood samples were collected. Mean cytokine levels and the difference between pretreatment levels and end of treatment levels were evaluated (Table 2). TNF-alpha and IL-1 beta levels decreased in both groups at the end of treatment, however this situation was more pronounced in GLN-supplemented group. The most obvious difference was observed in IL-6 and IL-8 levels. The change in IL-6 levels between the two groups is so obvious that it reveals itself with a statistical significance

Table 1. Changes of ETT*

ETT	GLN Group	Non-GLN Group	p value
Before treatment 1/3 (sec) After tretment 1/3 (sec)	2.06±1.34 3.78±6.03	5.78±14.49 8.81±16.09	0.77
Before treatment 2/3 (sec) After tretment 2/3 (sec)	19.68±32.66 10.37±14.52	24.56±33.92 36.96±44.50	0.03
Before treatment 3/3 (sec) After tretment 3/3 (sec)	26.68±40.83 17.37±30.65	20.09±31.69 39.21±44.11	0.59

*The transit time of upper part of esophagus (1/3 ETT), the transit time of middle part of esophagus (2/3 ETT), the transit time of lower part of esophagus (3/3 ETT). Total esophageal transit time of esophagus (ETT)

Table 2. Changes of TNF-alfa, IL-1beta, IL-6 and IL-8

	GLN Group	Non-GLN Group	p value
Before treatment TNFα	35.99±32.05	26.03±16.80	0.706
After treatment TNFα	26.01± 31.72	22.93±37.00	
Difference of TNFα	-10.02 ±32.68	-3.09±32.01	
Before treatment IL-1β	3.49±3.03	3.38±1.88	0.651
After treatment IL-1β	3.00± 2.22	2.90±1.59	
Difference of IL-1β	-0.48± 3.77	-0.47±2.25	
Before treatment IL6	93.99±102.15	31.32±33.95	0.019
After treatment IL6	44.63±80.71	55.92±68.81	
Difference of IL-6	-49.36± 83,72	24.58±69.04	
Before treatment IL8	374.15±466.72	191.24±250.80	0.346
After treatment IL8	210.93±360.54	189.32±226.70	
Difference of IL-8	-134.67±446.86	-1.9±349.88	

Table 3. The Initial Occurrence Time of Esophagitis, Total Time of Esophagitis and Maximum Esophagitis Grade

	GLN Group	Non-GLN Group	p value
The initial occurrence time of esophagitis (week)	3.12±0.99	2.28±1.13	0.382
Total time of esophagitis (week)	0.93±1.18	2.5±1.41	0.02
Maximum esophagitis grade	0.68±0.79	1.87±1.02	0.01

of p=0.019. Patients were also evaluated according to the time when esophagitis was first seen, total time of esophagitis and maximum esophagitis grade (Table 3).

Discussion

The purpose of this study was to assess the the efficacy of oral GLN in prevention of acute radiation-induced esophagitis in patients with lung cancer and to determine the predictive role of clinical (such as, serum immunological parameters and esophageal transit time) and dosimetric parameters.

In our study, no statistically significant relationship was found between esophagitis and the application of neoadjuvant chemotherapy. This result is supported by Singh et al.(Singh et al. 2003) studies. It was also reported that concurrent chemotherapy was likely to increase the risk of esophagitis (Rodriguez et al., 2009). In our study, of the 23 patients who received concomitant chemotherapy 17 patients (73.9%) developed esophagitis at one time during treatment, but this result was not statistically significant. In GLN- supplemented patients treated with chemoradiotherapy, esophagitis was observed in 53.8% of patients (7 patients). However, in GLN-non-supplemented group, incidence of esophagitis was 100% with chemoradiotherapy (p=0.051). This results supports the literature. Furthermore, there was no correlation between esophagitis and chemoradiotherapy in GLN-supplemented group. These results can be interpereted as follows: the risk of esophagitis is independent of the application of concomitant chemotherapy in GLN-supplemented group and concurrent chemotherapy does not increase the risk of esophagitis in this group. Rodriguez et al. (2009) reported that patients with lung cancer treated by chemoradiotherapy with the application of prophylactic GLN showed lowest risk of developing esophagitis compared to other studies. This report supports our results.

It is commonly assumed that the longer the length and volume of the esophagus segment included in the radiotheraphy field, the higher the probability of esophageal toxicity (Etiz et al., 2013), despite the fact that in the literature, different opinions have been expressed on this topic (Singh et al., 2003). It is not yet clear which parameters have a role in determining the development of esophagitis. In none of our grand total of patients did we find a relation between esophagitis and ratio of the length of esophagus in the field of treatment versus the total length of the esophagus. Neither did we find a relation between esophagitis and ratio of the volume of esophagus in the treatment field versus the total volume of esophagus. However, in GLN-supplemented group ratio of the length of esophagus in the field of treatment versus the total length of the esophagus was strongly related with esophagitis (p=0.041) whereas, there was no such significant relation in GLN-non-supplementedgroup. As a result, it can be interpreted that in this group of patients, there is an already developed esophagitis, regardless of length of the treatment field. There is no other study to investigating the relationship between these parameters and the development of esophagitis in GLN-supplemented patients, for which reason our results could not be compared with literature.

There are other studies investigating the relation between esophagitis and dosimetric parameters, such as the mean esophageal dose, maximum esophageal point dose (Jim et al., 2009; Etiz et al., 2013). In these studies, both of these parameters have been associated with the development of esophagitis. However, none of these studies applied any product to prevent the development of esophagitis in patients. In our study, we found no significant relationship between these parameters and the development of esophagitis either in all of our patients encompassing both study groups or in GLN-supplemented group. We found a strong relationship with statistical significance between maximum esophageal point dose and esophagitis in GLN-non-supplemented group (p=0.053) and the results of this group were consistent with the literature.

In reviewing the literature, there were many studies which examined the effect of esophageal dose-volume relationship on the development of esophagitis. Most of these studies reached different conclusions and there was no data about the relationship between dosimetric parameters and acute esophagitis (Rodriguez et al., 2009; Etiz et al., 2013). There was a clear relationship between dose-volume parameters and esophagitis however there were no absolute parameters associated with esophagitis. In our study, V20,V25,V30,V35,V40 and V45 parameters were statistically significantly associated with esophagitis in GLN-non-supplemented group (respectively; p=0.042, p=0.042, p=0.042, p=0.033, p=0.033, p=0.033). Looking at the overall group, this relationship is lost. This is interpreted as follows: 'Since esophagitis was significantly reduced by the effect of GLN, statistical significance was not found between the irradiated volume and esophagitis in the whole of the patients encompassing both groups'.

Topkan et al. investigated 41 lung cancer patients and 22 of them received prophylactic GLN. They investigated the effect of dose-volume parameters on the development of esophagitis, and they did not find any correlation between dose-volume parameters and esophagitis in their grand total of patients covering both GLN-supplemented and GLN-non-supplemented groups. However, they found a statistically significant relationship between severe esophagitis and esophageal V55 value (Topkan et al., 2009). These results confirm the results of our study.

In another 46-patient retrospective study, Tutanc et

al. aimed to understand the efficacy of oral GLN in the prevention of acute radiation-induced esophagitis in patients with lung cancer who are treated with thoracic radiotherapy. They reported the reduction of incidence and severity of acute radiation induced esophagitis during thoracic irradiation resulting from oral GLN with their datas (Tutanc et al., 2013).

A recent prospective randomized trial of oral GLN was conducted in patients of the head and neck cancer (Chattopadhyay et al., 2014). They showed that oral GLN delays the development of mucositis. The mean time of onset of mucositis was significantly delayed, the mean duration of grade 3 mucositis or worse (grade 3 and grade 4) and the mean total duration of mucositis were significantly less in patients who received oral GLN.

Esophageal scintigraphy is the gold standard technique for evaluation of the esophageal transit time (Iascone et al., 2004). Turkolmez et al. evaluated eighteen female patients with locally advanced inner quadrant breast cancer. A total dose of 5000 cGy in 25 fractions of 200 cGy was applied from four different portals to all patients. Esophageal motility was evaluated before and immediately after RT using esophageal scintigraphy. Post-irradiation therapy ETT values were significicantly higher compared to pre-radiation therapy ETT values ($p<0.001$) (Turkolmez et al., 2005). These results confirm the results of our study. In our study all of the transit times prolonged at the end of treatment. In subgroups analyzed, ETT was statistically significantly prolonged in GLN-non-supplemented group. There were no differrences in both groups before treatment, but at the end of treatment ETTs were significantly prolonged in GLN-non-supplemented group. We did not find any study investigating the relation between ETT and GLN supplementation.

Song et al. demonstrated that serum levels of TNF-α, IL-6, IL-8 and VEGF were all elevated in lung cancer patients, suggesting that inflammatory cytokines could be jointly used as a screening tool (Song et al., 2013). Also radiation induced side effects occur as a result of local irritation and inflammation in cancer patients. Inflammatory cytokines are involved in this process. As shown in cell cultures, GLN affects the production of cytokines such as TNF-alpha and interleukins which are released from macrophages and neutrophils. There were no human studies showing the effect of cytokines and therefore on inflamation with the use of GLN. However, in animal studies, a variety of cytokines were shown to be influenced by use of GLN. Amebo et al show that GLN supplementation provoked less damage and bacterial translocation and also lower concentrations of potent inflamatory cytokines IL-8 and TNF- α in rats with colitis (Amebo et al.,1997).

Our study is the first human study to examine the impact of the use of GLN on inflammatory cytokines. TNF-alpha and IL-1 beta levels decreased in both groups at the end of treatment, however this situation was more pronounced in GLN- supplemented group. The most obvious difference was observed in IL-6 and IL-8 levels. In GLN-non-supplemented group, IL-6 levels were significantly increased even at the end of treatment. The change in IL-6 levels between the two groups is so obvious that it reveals itself with a statistical significance of $p=0.019$.

It is known that cancer disease is thought to be effected by many inflammatory processes. This decrease in inflammatory markers with the application of GLN can be considered as an indication for its use in the weakening of inflammation in situations including cancer cachexia. Our results are important, because it is the first human study with the application of GLN resulting in significant reduction of inflammatory cytokines compared with the control group to which GLN supplementation was not administered.

Jiang et al. (2014) found that esophagitis was the most important factor for weight loss. In Veterans Administration Lung Group Protocols, the three most important prognostic factors identified to affect survival in patients with inoperable NSCLC were performance status, extent of disease, and weight loss (Stanley, 1980). Topkan et al. (2009) investigated 41 lung cancer patients and 22 of them received prophylactic GLN. Patients were evaluated for weight changes at the beginning and at the end of treatment, GLN-non-supplemented patients had significant weight loss whereas, GLN-supplemented patients had statistically significant weight gain. In our study, 37.5% of GLN-supplemented patients had weight loss but this rate was increased to 68.8% in GLN-non-supplemented cases. Additionally, 37.5% of GLN-supplemented patients had weight gain, but none of the patients gained weight in GLN-non-supplemented group. Our results showed statistical significance. As a result, less weight loss was observed with a decrease in inflammatory cytokines in GLN-supplemented group.

As a result of increasing use of multimodality treatment approaches, esophagitis has emerged as a significant dose limiting toxicity. Therefore, the primary strategy in controlling esophagitis involves the use of effective radioprotective agents. Amifostin has been studied as a radioprotector to decrease radiation induced toxicity in patients treated with RT for NSCLC (Antonadou et al., 2001). However, a larger, multi-institutional study (242 patients) by the Radiation Therapy Oncology Group failed to demonstrate an improvement in the esophageal tolerance (Wermer-Wasik et al., 2003). Topkan et al.demonstrated that both the incidence and severity of esophagitis was reduced by use of oral GLN in their study and they observed that the onset of esophagitis was significantly delayed (Topkan et al., 2009). Our current study suggests a beneficial role for oral GLN use in prevention and/or delay of esophagitis incidence and severity. We demonstrated that, GLN-supplemented group displayed a delay in occurrence of esophagitis and also total esophagitis time is reduced and maximum grade of esophagitis is lower in this group. Changes in the levels of proinflammatory cytokines and changes in the transit times of the esophagus were parallel to each other and showed conformity with the results of other toxicity studies. TNF-alpha and IL-1 beta, IL-6 and IL-8 levels decreased in GLN-supplemented group at the end of treatment. The change in IL- 6 levels between the two groups was so obvious that it revealed itself with a statistical significance. Due to the significantly shorter ETT and reduction of esophageal side effects,

we concluded in this study that GLN supplementation reduces local inflammation and motility disorders due to the reduction of inflammatory cytokines. Currently, there are no studies demonstrating prevention of acute esophagitis development via reduced inflammation and motility disorder through GLN supplementation. Hence, our results could not be compared with the literature.

In conclusion, the results of this study suggest a beneficial role of oral GLN use in prevention and/or delay of esophagitis incidence and severity due to suppression of the inflammatory process in lung cancer patients treated with definitive RT. In this way, toxicity was reduced and treatment-induced weight loss was decreased. These findings may potentially contribute positively on treatment results and quality of life (QOL) in patients treated with intensive regimens. Therefore, GLN can be recommended for patients with lung cancer that receive RT. Our study will guide further studies.

References

Ahn SJ, Kahn D, Yu X, et al (2005). Dosimetric and clinical predictors for radiation-induced esophageal injury. *Int J Radiat Oncol Biol Phys*, **61**, 335-47.

Antonadou D, Coliarakis N, Synodinou M, et al (2001). Randomized phase III trial of radiation treatment±amifostine in patients with advanced stage lung cancer. *Int J Radiat Oncol Biol Phys*, **51**, 915-22.

Amebo, AA Adjei, EK Harrison, et al (1997). Prophylactic effect of dietary GLN supplementation on interleukin 8 and tumour necrosis factor alpha production in trinitrobenzene sulphonic acid induced colitis. *Gut*, **41**, 487-93.

Bradley J (2005). A review of radiation dose escalation trials for non-small cell lung cancer within the Radiation Therapy Oncology Group. *Semin Oncol*, **32**, 111-3.

Belderbos J, Heemsbergen W, Hoogeman M, et al (2005). Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy. *Radiother Oncol*, **75**, 157-64.

Chattopadhyay S, Saha A, Azam M, et al (2014). Role of oral glutamine in alleviation and prevention of radiation-induced oral mucositis: A prospective randomized study. *South Asian J Cancer*, **3**, 8-12.

Choy H, Akerley W, Safran H, et al (1998). Multiinstitutional phase II trial of paclitaxel, carboplatin, and concurrent radiation therapy for locally advanced non-small cell lung cancer. *J Clin Oncol*, **16**, 3316-22.

Topkan E, Yavuz MN, Onal C, et al (2009). Prevention of acute radiation-induced esophagitis with GLN in non-small cell lung cancer patients treated with radiotherapy: Evaluation of clinical and dosimetric parameters, *Lung Cancer*, **63**, 393-9.

Etiz D, Bayman E, Akcay M, et al (2013). Dosimetric and clinical predictors of acute esophagitis in lung cancer patients in turkey treated with radiotherapy. *Asian Pac J Cancer Prev*, **14**, 4223-8.

Huang EY, Wan Leung S, Wang CJ, et al (2000). Oral GLN to alleviate radiation-induced oral mucositis: A pilot randomized trial. *Int J Radiat Oncol Biol Phys*, **46**, 535-9.

Iascone C, Di Giulio E, Maffi C, et al (2004). Use of radioisotopic esophageal transit in the assessment of patients with symptoms of reflux and non-specific esophageal motor disorders. *Dis Esophagus*, **17**, 218-22.

Jiang N, Zhao JZ, Chen XC, et al (2014). Clinical determinants of weght loss in patients with esophageal carcinoma during radiotherapy: a prospective longitudinal view. *Asian Pac J Cancer Prev*, **15**, 1943-8.

Rose J, Rodrigues G, Yaremko B, et al (2009). Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. *Radiother Oncol*, **91**, 282-7.

Kuhn KS, Muscaritoli M, Wischmeyer P, et al (2010). GLN as indispensable nutrient in oncology: experimental and clinical evidence. *Eur J Nutr*, **49**, 197-210.

Plata-Salaman CR, Oomura Y, Kai Y (1998). Tumor necrosis factor and interleukin 1 Beta: suppression of flood intake by direct action in the central nervous system. *Brain Res*, **448**, 106-14.

Rodriguez N, Algara M, Fora P, et al (2009). Predictors of acute esophagitis ın lung cancer patients treated with concurent three-dimensional conformal radiotherapy and chemotherapy. *Int J Radiat Oncol Biol Phys*, **73**, 810-7.

Sasso G, Rambaldi P, Sasso FS et al (2008). Scintigraphic evaluation of esophageal transit during radiotherapy to the mediastinum. *BMC Gastroenterology*, **8**, 51.

Shih A, Miaskowski C, Dodd M, et al (2003). Mechanisms for radiation-induced oral mucositis and the consequences. *Cancer Nursing*, **26**, 222-9.

Singh AK, Lockett MA, Bradley JD (2003). Predictors of radiation-induced esophageal toxicity in patients with nonsmall-cell lung cancer treated with three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys*, **55**, 337-41.

Song XY, Zhou SJ, Xiao N, et al (2013). Research on the relationship between serum levels of inflammatory cytokines and non-small cell lung cancer. *Asian Pac J Cancer Prev*, **14**, 4765-8.

Stanley KE (1980). Prognostic factors for survival in patients with inoperable lung cancer. *J Natl Cancer Inst*, **65**, 25-32.

Tutanc OD, Aydogan A, Akkucuk S, et al (2013). The efficacy of oral glutamine in prevention of acute radiotherapy-induced esophagitis in patients with lung cancer. *Contemp Oncol (Pozn)*, **17**, 520-4.

Turkolmez S, Atasever T, Akmansu M (2005). Effects of radiation therapy on esophageal transit in patients with inner quadrant breast tumour. *Nucl Med Commun*, **26**, 721-6.

Wermer- Wasik M, Scott C, Movsas B, et al (2003). Amifostine as mucosal protectant in patients with locally advanced non-small cell lung cancer (NSCLC) receiving intensive chemotherapy and thoracic radiotherapy (RT): results of the radiation therapy oncology group (RTOG) 98-01 study. *Int J Radiat Oncol Biol Phys*, **57**, 216.