

Use of oral glutamine in radiation-induced adverse effects in patients with thoracic and upper aerodigestive malignancies: Results of a prospective observational study

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Abstract. Cancer growth in host tissues features glutamine (gln) depletion over time, decreasing epithelial cells' optimal functioning. In addition, radiotherapy (RT) and/or chemotherapy (CT) cause damage to normal tissues, probably enhanced by this depletion. The present study prospectively examined the effect of gln supplementation on 72 patients with thoracic and upper aerodigestive malignancies (T&UAM) treated with sequential or concurrent RT-CT or RT alone. All patients received prophylactic gln powder 15 g bid for the full duration of treatment. The severity of acute radiation toxicities was graded according to the RT Oncology Group/European Organization for Research and Treatment of Cancer criteria. Primary endpoints were the incidence of grade >2 toxicities, weight loss and requirement for analgesics, and the secondary

endpoint was the association of the length of irradiated esophagus from treatment planning with the use of opioids. The incidence of adverse effects was as follows: Grade >2 stomatitis, 25.0%; esophagitis, 60.5%; dysphagia, 54.2%; pain, 25.4%; mycosis, 40.8%. Stomatitis grade >2 was more frequent in patients with head and neck tumors ($P<0.001$) and in those with prior surgery ($P<0.001$). Esophagitis ($P=0.020$) and dysphagia ($P=0.008$) grade >2 were more frequent in patients with concurrent RT-CT. Regarding analgesics, 9.9% of patients received no pain treatment, 56.3% received simple analgesic therapy and 33.8% opioids. Patients on opioid therapy had a greater mean length of irradiated esophagus ($P=0.024$) or length >12 cm ($P=0.018$). In 54.2% of patients, weight loss was observed, particularly with concurrent RT-CT ($P=0.007$). Thus, the use of oral gln may have an important role in reducing acute radiation toxicities and weight loss, and in lowering the requirement for analgesics in patients with T&UAM. Further randomized trials are required to identify the appropriate gln dose, duration of treatment and precise radiation dosimetric parameters in this group of patients. The present clinical trial was retrospectively registered in the ClinicalTrials.gov Protocol Registration and Results System (registration no. NCT05054517/22-09-2021).

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Abbreviations: gln, glutamine; RT, radiotherapy; CT, chemotherapy; H&NT, head and neck tumors; T&UAM, thoracic and upper aerodigestive malignancies; TCA, tricarboxylic acid; RCT, randomized controlled trial; LC, lung cancer; ALL, acute lymphoblastic leukemia; ARIE, acute RT-induced esophagitis; NSCLC, non-small cell LC; OM, oral mucositis

Key words: glutamine, chest tumor, lung cancer, head and neck cancer, clinical study, human subjects

Introduction

Glutamine (gln) is the most abundant free amino acid in the body, held within skeletal muscle cells. Gln is used by the cell for both bioenergetic and biosynthetic needs. Once taken up by the cell, the vast majority of gln is converted to glutamate by mitochondrial glutaminase, an enzyme whose levels are frequently upregulated in tumors and tumor cell lines (1,2).

Proliferatively active cells require a source of carbon and nitrogen for the synthesis of macromolecules. Although most

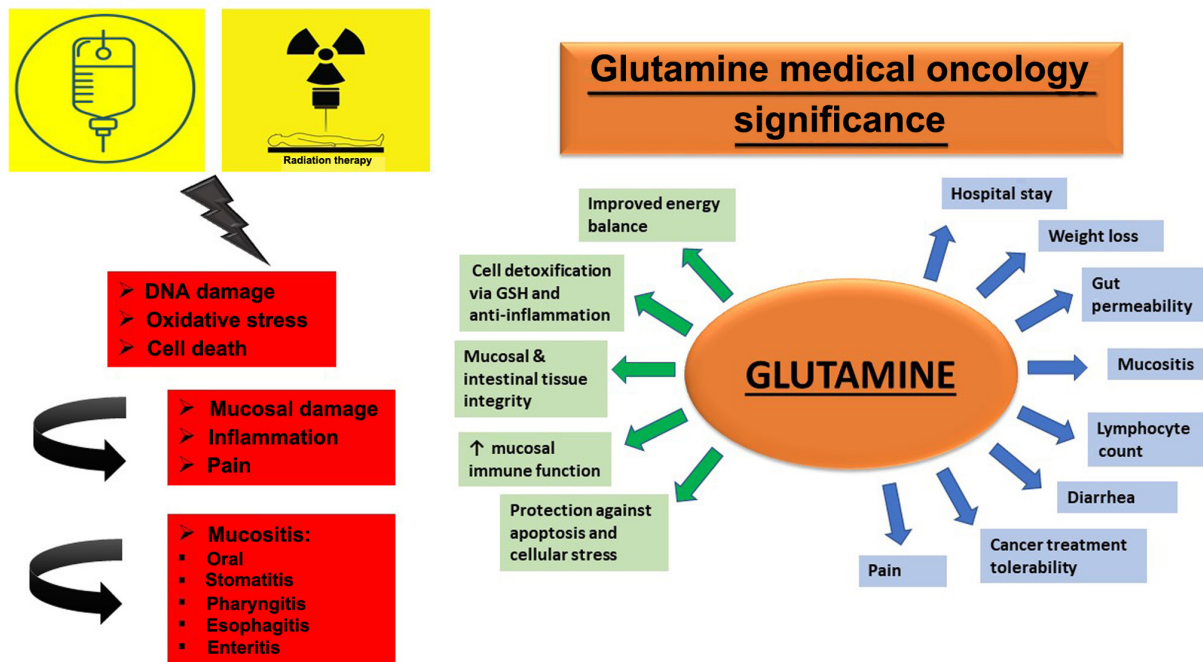


Figure 1. Medical oncology significance of gln. Gln has effects on mucositis/stomatitis, esophagitis, diarrhea, weight loss, gut permeability, lymphocyte count, hospital stay and pain. Gln, glutamine; GSH, glutathione.

tumor cells utilize aerobic glycolysis and shunt metabolites away from mitochondrial oxidative phosphorylation, numerous tumor cells exhibit increased mitochondrial activity. In these cells, gln uptake is markedly enhanced and far exceeds the metabolic requirements of the cell (3).

In the case of tumor growth and proliferation, a single conceptual model of the cancer metabolism program does not exist. Variability exists across different types of cancer in terms of glycolytic and glutaminolytic contribution to malignant proliferation, which allows tumors to utilize different anaplerotic precursors or metabolic platforms as a means of dynamic adaptation under stress (4).

Cancer cells exhibit dysregulation of the proteins/enzymes involved in the key regulatory steps of glucose transport, glycolysis, tricarboxylic acid (TCA) cycle and glutaminolysis, governed not only by oncogenes such as c-Myc but also by hypoxia-inducible factor-1 and loss of function tumor suppressor p53 (5). The MYC oncogene, which serves a critical role in numerous types of human cancer, is considered a master regulator of cell metabolism and proliferation, reprogramming mitochondrial metabolism towards sustaining cellular viability and TCA cycle anaplerosis (6).

Numerous *in vitro* studies provided evidence that upregulation of the gln pathway provides cancer cells with a variety of essential products to sustain cell proliferation, such as ATP and macromolecules, for biosynthesis. Human cancer cell lines exhibited a 5- to 10-fold faster rate of gln consumption than non-malignant cells (7). It may be inferred that available gln predicts a more aggressive tumor behavior and raises the possibility that nutritional supplementation with gln may stimulate tumor growth by promoting angiogenesis, survival and motility of cancer cells through the activation of NF- κ B (8). Several gln analogs have been studied as

potential chemotherapeutic (CT) agents in preclinical animal studies and in phase I clinical trials in patients with the rationale to diminish blood gln levels and, thereby, decrease the availability of gln to the tumor; however, the results were disappointing, and studies were discontinued due to side effects (9). On the contrary, in rat model studies, supplemental oral gln improved host tolerance through altering glutathione metabolism and protected normal tissues from CT treatment-related injury (10).

These contradictory results of *in vitro* and animal studies clearly indicate that reliable information regarding the effects of supplemental gln may only be made based on clinical studies in humans. If gln is not available from exogenous sources, tumor cells may manipulate the host metabolism to cover their needs endogenously. Thus, any measures to establish a gln depletion situation ‘artificially’ cannot stop or even retard tumor growth (11). Furthermore, the endogenous use of gln by parasitic cancer cells is associated with impaired physiological functions of disturbed mucosal integrity and diminished immune competence (12).

With this hypothesis, within the last two decades, numerous clinical trials evaluated supplemental oral, enteral, or parenteral gln tolerance, safety and effects in various cancer patient groups; dosage, time, and frequency of gln supplementation, as well as cancer type and stage of disease, varied considerably (13). In general, oral/enteral and parenteral gln dipeptide supplementation was safe and well-tolerated, with tumor growth and tumor protein synthesis being unaltered and with no adverse effects on the efficacy of antitumor treatment (14).

Concerning gln supplementation, >50 clinical studies for all cancer types (from the MEDLINE Database between 2000 and 2020) have been performed. For patients with thoracic and upper aerodigestive malignancies (T&UAM), 22 clinical studies with oral gln supplementation [16 randomized

Table I. Patient characteristics and features of their disease and treatment.

Variable	Value
Age, years	65.6±11.2
Sex	
Male	54 (75.0)
Female	18 (25.0)
Weight loss after RT	
No	30 (42.3)
Yes	41 (57.7)
PS	
0	29 (40.3)
1	37 (51.4)
2	6 (8.3)
Cancer type	
Chest tumor	33 (45.8)
Head & neck	39 (54.2)
Grade	
1	7 (11.7)
2	24 (40.0)
3	29 (48.3)
Stage	
I	11 (15.9)
II	12 (17.4)
III	37 (53.6)
IV	9 (13.0)
Duration of RT, days	33.6±13.0
Total dose, cGY	5,489.4±1,196.2
Irradiation fractions	26.4±7.1
Length of the radiated esophagus from treatment planning, cm	12.4±3.3
Length of the radiated esophagus from treatment planning (cm)	
<12	31 (43.7)
>12	40 (56.3)
Prior surgery	25 (34.7)
Prior chemotherapy	31 (43.7)
Concurrent chemotherapy	27 (38.0)
Chemotherapy (before and at the same time as RT)	14 (19.7)
Chemotherapy only at the same time as RT	13 (18.3)
Only RT	27 (38.0)
Subsequent chemotherapy after RT	21 (29.6)
Smoking	
No	19 (26.4)
Yes	43 (59.7)
Former smoker	10 (13.9)
Alcohol consumption	28 (41.8)
Diabetes	20 (31.7)
Hypertension	30 (54.5)

Values are expressed as n (%) or the mean ± standard deviation. PS, performance status; RT, radiotherapy.

Table II. Grading system for pain medications.

Grade ^a	Drug	Group
0	None	No
1	Simple analgesics	Simple analgesics and/or NSAIDs
2	Simple analgesics and NSAIDs	Simple analgesics and/or NSAIDs
3	Weak narcotics, i.e., codeine	Opioids
4	Narcotics, i.e., fentanyl patch	Opioids

^aWorld Health Organization's pain relief ladder (17). NSAIDs, non-steroidal anti-inflammatory drugs.

controlled trials (RCTs), 3 pilot and 3 retrospective studies] evaluated its safety, tolerance and effect on mucositis/stomatitis, esophagitis, pain, weight loss and hospital stay. According to most of the available clinical evidence, gln supplementation may decrease the incidence and/or severity of standard of care treatment-associated toxicities in tumors of the lung and esophagus, as well as head & neck tumors (H&NT) (13,15), while dosimetric modality parameters impacting this effect remain to be clarified and this effect remains to be translated into the need for analgesic therapy (Fig. 1).

Therefore, the present study aimed to evaluate the potential effect of oral gln to reduce radiation-induced toxicities, weight loss and pain in patients with T&UAM. In addition, to define a subgroup of patients who are more likely to benefit from treatment, association with dosimetric parameters predictive of these adverse effects, such as the length of the irradiated esophagus, were determined. The primary endpoints were the incidence of toxicities of grade 2, weight loss and the need for analgesic therapy. The secondary endpoint was the correlation of the length of the irradiated esophagus from radiotherapy (RT) treatment planning with the use of opioids as analgesics.

Materials and methods

Study subjects. A total of 72 patients with biopsy-confirmed T&UAM, treated either with sequential or concomitant RT-CT (62%) or RT alone (38%) and supplemented with oral gln prior to the initiation of the RT treatment were prospectively recruited from the Department of Radiation Oncology of Athens Medical Center (Athens, Greece) between April 2013 and September 2017. Sample size calculation was not performed a priori since it was restricted by the sample availability. The mean age of the patients was 65.6±1.2 years (age range, 54-77 years). Most participants were males (n=54, 75%). Table I provides demographics and clinical characteristics of the patients. The study was approved by the Ethics Committee of the Hospital (approval no. 2281/26-04-2013).

Demographics and clinical characteristics. Patient characteristics and features of their disease and treatment

Table III. Adverse events and pain treatment.

Item	n (%)
Stomatitis, grade	
0	41 (60.3)
1	10 (14.7)
2	9 (13.2)
3	8 (11.8)
Esophagitis, grade	
0	8 (11.3)
1	20 (28.2)
2	28 (39.4)
3	15 (21.1)
Dysphagia, grade	
0	9 (12.9)
1	23 (32.9)
2	33 (47.1)
3	5 (7.1)
Pain, grade	
0	8 (11.3)
1	45 (63.4)
2	7 (9.9)
3	11 (15.5)
Mycosis	
No	42 (59.2)
Yes	29 (40.8)
At least one adverse event	
No	7 (10.4)
Yes	60 (89.6)
Pain treatment	
None	7 (9.9)
Simple analgesics	40 (56.3)
Simple analgesics and opioids	12 (16.9)
Opioids	12 (16.9)
Antimycotic treatment	
No	42 (59.2)
Yes	29 (40.8)
Antimycotic prophylaxis	
No	40 (61.5)
Yes	25 (38.5)

are presented in Table I, more than half of the participants (54.2%) had H&NT, while the remaining (45.8%) had tumors of the chest, i.e. lung cancer (LC). In addition, 40.0% of the participants had grade 2 cancer and 53.6% were in stage III. The mean duration of RT was 33.6 ± 13.0 days and in 56.3% of the cases, the length of the irradiated esophagus from treatment planning was >12 cm. A total of 34.7% of the patients had previous surgery and 43.7% had a CT prior to RT. Furthermore, 19.7% of the patients had CT

prior to and at the same time as RT, while 18.3% had CT only at the same time as RT (concurrent CT-RT). A total of 57.7% of the participants had lost weight after the RT and the majority had a performance status (PS) of <2 . Diabetes and hypertension were present in 31.7% and 54.5% of the patients, respectively.

Patient treatment. All participants were treated either with sequential or concomitant RT-CT (62%) or RT alone (38%) and received prophylactic gln powder in doses of 15 g 2 times per day (bid), for the total duration of RT treatment. The radiation technique was three-dimensional conformal RT. Prior to RT, patients had a computerized tomography scan on the region of the body treated using adequate immobilization. Clinical treatment volumes, planning treatment volumes and organs at risk were contoured on each slice (3 mm/5 mm) with isodose distribution on the nasopharynx or mediastinum, also displaying the length of the irradiated esophagus. 3D plans were generated on a Masterplan (Nucletron Group Ltd.) treatment planning system using the collapsed cone algorithm. Irradiation was then performed using a 6MV Primus (Siemens AG) linear accelerator with a total dose of 50-70 Gy and 2-2.5 Gy/fraction. Concurrent CT consisted of low-dose weekly cisplatin in 38% of the patients.

The severity of different acute radiation toxicities was graded according to the RT Oncology Group/European Organization for Research and Treatment of Cancer criteria (16). The median follow-up of the acute radiation toxicities was one month, as for the duration of gln supplementation. For each patient, the medical history was reviewed and clinical examination was performed.

Smoking history and alcohol use were marked as risk factors and diabetes and hypertension as comorbidities, while stomatitis, esophagitis, dysphagia, pain and mycosis were reported as acute adverse events of RT.

Medications for pain control were prescribed when the patient became symptomatic. Antimycotic treatment was given in clinical fungal infection, while antimycotic prophylactic therapy was given in patients with a high probability of displaying one [patients with a high grade of oral mucositis (OM), pain and dysphagia]. Table II provides the grading system for pain medications, following the World Health Organization's pain relief ladder (17).

Statistical analysis. Quantitative variables are presented as mean values \pm standard deviation, while qualitative variables are presented as frequencies with percentages (%). For comparison of proportions, Pearson's χ^2 and Fisher's exact tests were used. Student's t-tests were applied for comparison of continuous variables between the groups. Logistic regression analysis in a stepwise method (for entry, $P=0.05$; for removal, $P=0.10$) was performed to identify independent factors associated with weight loss after RT. Adjusted odds ratios (OR) with the corresponding 95% confidence intervals (95% CI) were calculated from logistic regression analyses. All reported P-values were two-tailed and $P<0.05$ was considered to indicate statistical significance. Analyses were performed using SPSS statistical software (version 19.0; IBM Corporation).

Table IV. Occurrence of stomatitis, esophagitis and dysphagia in association with demographics and clinical characteristics.

Item	Stomatitis (grade)			P-value	Esophagitis (grade)			P-value	Dysphagia (grade)			P-value
	0/1	2/3			0/1	2/3			0/1	2/3		
Age, years	65.8±10.3	62.6±13.7		0.314 ^a	65.6±11	65.3±11.4		0.888 ^a	65.8±11.0	64.7±11.3		0.675 ^a
Sex				0.053 ^b				0.615 ^c				0.500 ^c
Male	41 (82.0)	9 (18.0)			20 (37.7)	33 (62.3)			25 (48.1)	27 (51.9)		
Female	10 (55.6)	8 (44.4)			8 (44.4)	10 (55.6)			7 (38.9)	11 (61.1)		
PS				0.066 ^c				0.781 ^c				0.281 ^c
0	25 (86.2)	4 (13.8)			12 (41.4)	17 (58.6)			15 (53.6)	13 (46.4)		
1/2	26 (66.7)	13 (33.3)			13 (38.1)	26 (61.9)		0.146 ^c	17 (40.5)	25 (59.5)		0.104 ^c
Cancer type				<0.001 ^c								
Chest tumors	30 (100.0)	0 (0.0)			16 (48.5)	17 (51.5)			18 (56.3)	14 (43.8)		
Head neck	21 (55.3)	17 (44.7)			12 (31.6)	26 (68.4)		0.113 ^c	14 (36.8)	24 (63.2)		0.123 ^c
Grade				0.211 ^c								
1/2	24 (80.0)	6 (20.0)			17 (54.8)	14 (45.2)			19 (61.3)	12 (38.7)		
3	19 (65.5)	10 (34.5)			10 (34.5)	19 (65.5)		0.888 ^c	12 (41.4)	17 (58.6)		0.668 ^c
Stage				0.100 ^c								
I/II	19 (86.4)	3 (13.6)			9 (40.9)	13 (59.1)			11 (50.0)	11 (50.0)		
III/IV	29 (67.4)	14 (32.6)			18 (39.1)	28 (60.9)		0.001 ^a	20 (44.4)	25 (55.6)		0.006 ^a
Duration of RT, days	33.6±12.4	32.7±15.7		0.804 ^a	27.1±12.2	38±11.8		0.105 ^a	29.3±12.9	38±11.6		0.199 ^a
Total dose, cGY	5,414.7±1,128.1	5,817.6±1,388.2		0.233 ^a	5,203.9±1,193.8	5,675.3±1,174.2		0.138 ^a	5,329.1±1,167.1	5,690±1,155.3		0.304 ^a
Irradiation fractions	26.0±7.0	28.6±6.8		0.188 ^a	24.9±7.2	27.4±6.8		0.453 ^a	25.8±7.2	27.4±6.5		0.229 ^a
Length of the radiated esophagus from treatment planning, cm	12±2.8	13.4±4.5		0.124 ^a	12.1±3.3	12.7±3.3			11.9±2.9	12.8±3.5		
Length of the radiated esophagus from treatment planning, cm				0.325 ^c				0.174 ^c				0.172 ^c
<12	25 (80.6)	6 (19.4)			15 (48.4)	16 (51.6)			17 (54.8)	14 (45.2)		
>12	26 (70.3)	11 (29.7)			13 (32.5)	27 (67.5)		0.431 ^c	15 (38.5)	24 (61.5)		0.623 ^c
Prior surgery				<0.001 ^c								
No	40 (90.9)	4 (9.1)			17 (36.2)	30 (63.8)			22 (47.8)	24 (52.2)		
Yes	11 (45.8)	13 (54.2)			11 (45.8)	13 (54.2)		0.385 ^c	10 (41.7)	14 (58.3)		0.377 ^c
Prior chemotherapy				0.255 ^c								
No	28 (70.0)	12 (30.0)			14 (35.0)	26 (65.0)			16 (41.0)	23 (59.0)		
Yes	23 (82.1)	5 (17.9)			14 (45.2)	17 (54.8)			16 (51.6)	15 (48.4)		

Table IV. Continued.

Item	Stomatitis (grade)		P-value	Esophagitis (grade)		P-value	Dysphagia (grade)		P-value
	0/1	2/3		0/1	2/3		0/1	2/3	
Concurrent chemotherapy			0.044 ^c			0.020 ^c			0.008 ^c
No	35 (83.3)	7 (16.7)		22 (50.0)	22 (50.0)		25 (58.1)	18 (41.9)	
Yes	16 (61.5)	10 (38.5)		6 (22.2)	21 (77.8)		7 (25.9)	20 (74.1)	
Only RT			0.317 ^c			0.239 ^c			0.122 ^c
No	29 (70.7)	12 (29.3)		15 (34.1)	29 (65.9)		17 (38.6)	27 (61.4)	
Yes	22 (81.5)	5 (18.5)		13 (48.1)	14 (51.9)		15 (57.7)	11 (42.3)	
Subsequent chemotherapy			0.649 ^c			0.225 ^c			0.059 ^c
No	36 (76.6)	11 (23.4)		22 (44.0)	28 (56.0)		26 (53.1)	23 (46.9)	
Yes	15 (71.4)	6 (28.6)		6 (28.6)	15 (71.4)		6 (28.6)	15 (71.4)	

^aStudent's t-test; ^bFisher's exact test; ^cPearson's χ^2 test. Values are expressed as n (%) or the mean \pm standard deviation. PS, performance status; RT, radiotherapy.

Results

Adverse events and pain treatment. The frequencies of patients with adverse events and pain treatment are presented in Table III. In 39.7% of the patients, stomatitis was grade 1 or more and the frequencies for esophagitis, dysphagia and pain were 88.7, 87.1 and 88.7%, respectively. Mycosis was present in 40.8% of the patients (all of them manages with antimycotic treatment) and 89.6% had at least one adverse event. Opioids were used in 16.9% of the cases and in 16.9% of the cases, the combination of both simple analgesics and opioids was utilized. In total, opioids were used in 33.8% of the study population.

Association between adverse events and patient characteristics. The occurrence of stomatitis, esophagitis and dysphagia in association with demographics and clinical characteristics are presented in Table IV. Stomatitis grade 2 to 3 was more frequent in H&NT (P=0.001), in those having previous surgery (OR: 11.818; 95% CI: 3.207-43.550; P<0.001) and in those having concurrent CT (OR: 3.125; 95% CI: 1.007-9.699; P=0.044). Esophagitis (OR: 3.500; 95% CI: 1.185-10.335; P=0.020) and dysphagia (OR: 3.968; 95% CI: 1.385-11.369; P=0.008) grade 2 to 3 was more frequent in those having concurrent CT-RT (Table SI). In addition, the duration of RT was indicated to be significantly greater in patients with esophagitis (P=0.001) and dysphagia (P=0.006) grades 2 to 3. Furthermore, it was indicated (data not shown) that patients who consume alcohol had grade 2-3 esophagitis in a significantly greater percentage compared to the ones who did not consume any alcohol (78.6 vs. 48.7%; P=0.013). In addition, patients who consumed alcohol had grade 2-3 dysphagia in a significantly greater percentage compared to the ones who did not consume any alcohol (71.4 vs. 42.1%; P=0.018). In addition, grade 2-3 dysphagia was present in a significantly greater percentage of patients with diabetes than in those without diabetes (70.0 vs. 38.1%; P=0.019).

Pain and opioid use. Table V presents the frequencies of patients with pain, mycosis and at least one adverse event according to demographics and clinical characteristics. Pain grade 2 to 3 (OR: 5.067; 95% CI: 1.608-15.967; P=0.004) and mycosis (OR: 6.000; 95% CI: 2.096-17.173; P=0.001) were more frequent in those having concurrent CT-RT. Mycosis was more frequent in cases with PS 1 to 2 (OR: 4.640; 95% CI: 1.569-13.728; P=0.004). Pain grade 2 to 3 (OR: 3.417; 95% CI: 1.108-10.553; P=0.028) and mycosis (OR: 4.667; 95% CI: 1.568-13.886; P=0.004) were also more frequent in those having CT after RT, while the proportion of subjects with mycosis was lower in those treated with RT only (OR: 0.350; 95% CI: 0.123-0.994; P=0.045; Table SI).

A total of 40 patients (56.3%) received only simple analgesics for pain treatment, while opioid therapy with or without analgesics was taken by 24 patients (33.8%). A total of 7 patients (9.9%) did not report any pain and received no pain treatment (Table III). The mean length of the irradiated esophagus from treatment planning (P=0.024) and duration of RT (P=0.023) were significantly greater in those to whom opioids were administered (Table VI). The use of opioids was

Table V. Proportion of patients with pain, mycosis and at least one adverse event according to demographics and clinical characteristics.

Item	Pain (grade)			Mycosis		At least one adverse event	
	0-1	2-3	P-value	No	Yes	No	Yes
Age, years	66±11.5	63.7±10.3	0.462 ^a	65.6±10.9	65.1±11.7	66.7±12.1	64.6±1.1
Sex			0.763 ^b				
Male	40 (75.5)	13 (24.5)		34 (64.2)	19 (35.8)	4 (8.2)	45 (91.8)
Female	13 (72.2)	5 (27.8)		8 (44.4)	10 (55.6)	3 (16.7)	15 (83.3)
PS			0.192 ^c				
0	24 (82.8)	5 (17.2)		23 (79.3)	6 (20.7)	4 (14.3)	24 (85.7)
1/2	29 (69.0)	13 (31.0)		19 (45.2)	23 (54.8)	3 (7.7)	36 (92.3)
Cancer type			0.066 ^c				
Chest tumor	28 (84.8)	5 (15.2)		22 (66.7)	11 (33.3)	3 (10.3)	26 (89.7)
Head & neck	25 (65.8)	13 (34.2)		20 (52.6)	18 (47.4)	4 (10.5)	34 (89.5)
Grade			0.111 ^c				
1/2	25 (80.6)	6 (19.4)		22 (71.0)	9 (29.0)	5 (16.7)	25 (83.3)
3	18 (62.1)	11 (37.9)		14 (48.3)	15 (51.7)	1 (3.4)	28 (96.6)
Stage			0.284 ^c				
I/II	18 (81.8)	4 (18.2)		16 (72.7)	6 (27.3)	4 (18.2)	18 (81.8)
III/IV	32 (69.6)	14 (30.4)		24 (52.2)	22 (47.8)	3 (7.1)	39 (92.9)
Duration of RT, days	32.6±14.0	36.2±9.4	0.330 ^a	31.3±13.7	37±11.3	33.6±4.7	33.7±13.8
Total dose, cGY	5,384.9±1,219.1	5,797.2±1,100.5	0.209 ^a	5,340.0±1,192.4	5,705.9±1,188.7	5,214.3±1,120.2	5,592.5±1,176.6
Irradiation fractions	25.7±7.4	28.6±5.8	0.142 ^a	25.5±7.4	27.7±6.5	26.3±5.5	27±6.9
Length of the radiated esophagus from treatment planning, cm	12.2±3.0	13.1±4.0	0.297 ^a	12.1±3.0	12.9±3.6	11.3±2.6	12.5±3.4
Length of the radiated esophagus from treatment planning, cm			0.637 ^c				
<12	24 (77.4)	7 (22.6)		21 (67.7)	10 (32.3)	5 (16.1)	26 (83.9)
>12	29 (72.5)	11 (27.5)		21 (52.5)	19 (47.5)	2 (5.6)	34 (94.4)
Prior surgery			0.598 ^c				
No	36 (76.6)	11 (23.4)		29 (61.7)	18 (38.3)	5 (11.6)	38 (88.4)
Yes	17 (70.8)	7 (29.2)		13 (54.2)	11 (45.8)	2 (8.3)	22 (91.7)
Prior chemotherapy			0.637 ^c				
No	29 (72.5)	11 (27.5)		23 (57.5)	17 (42.5)	5 (12.8)	34 (87.2)
Yes	24 (77.4)	7 (22.6)		19 (61.3)	12 (38.7)	2 (7.1)	26 (92.9)

Table V. Continued.

Item	Pain (grade)		P-value	Mycosis		P-value	At least one adverse event		P-value
	0-1	2-3		No	Yes		No	Yes	
Concurrent chemotherapy									
No	38 (86.4)	6 (13.6)	0.004 ^e	33 (75.0)	11 (25.0)	0.001 ^c	4 (9.8)	37 (90.2)	1.000 ^b
Yes	15 (55.6)	12 (44.4)		9 (33.3)	18 (66.7)		3 (11.5)	23 (88.5)	
Only RT									
No	30 (68.2)	14 (31.8)	0.110 ^e	22 (50.0)	22 (50.0)	0.045 ^c	3 (7.3)	38 (92.7)	0.417 ^b
Yes	23 (85.2)	4 (14.8)		20 (74.1)	7 (25.9)		4 (15.4)	22 (84.6)	
Subsequent chemotherapy									
No	41 (82.0)	9 (18.0)	0.028 ^e	35 (70.0)	15 (30.0)	0.004 ^c	6 (13.0)	40 (87.0)	0.419 ^b
Yes	12 (57.1)	9 (42.9)		7 (33.3)	14 (66.7)		1 (4.8)	20 (95.2)	

^aStudent's t-test; ^bFisher's exact test; ^cPearson's χ^2 test. Values are expressed as n (%) or the mean \pm standard deviation. PS, performance status; RT, radiotherapy.

^aStudent's t-test; ^bFisher's exact test; ^cPearson's χ^2 test. Values are expressed as n (%) or the mean \pm standard deviation. PS, performance status; RT, radiotherapy.

more frequent in cases where the length of the irradiated esophagus from treatment planning was >12 cm ($P=0.018$; Table VI). Contrarily, the use of opioids was less frequent in patients with stomatitis grade 0-1 (OR: 6.667; 95% CI: 2.012-22.085; $P=0.001$) and in patients with pain grade 0-1 (OR: 4.835; 95% CI: 1.553-15.052; $P=0.005$; Table VII).

Weight loss. The percentages of patients who lost weight after RT are presented in Table VIII. Significantly greater were weight loss percentages in patients with H&NT (OR: 2.6; 95% CI: 0.987-6.846; $P=0.051$), in those who had concurrent CT (OR: 4.2; 95% CI: 1.420-12.419; $P=0.007$) and in those who had CT after the RT (OR: 3.2; 95% CI: 1.016-10.076; $P=0.041$). In addition, the duration of RT ($P=0.001$), total dose in cGY ($P<0.001$), irradiation fractions ($P<0.001$) and length of the irradiated esophagus from treatment planning ($P=0.009$) were significantly greater in patients with weight loss. When multiple logistic regression analysis was applied with weight loss as the dependent variable, a significant association with the total dose of RT and concurrent CT-RT was observed and larger doses of RT resulted in a higher likelihood of weight loss (OR: 1.08; 95% CI: 1.02-1.14; $P=0.007$). In addition, patients with concurrent CT-RT had a higher weight loss likelihood (OR: 3.21; 95% CI: 1.03-10.0; $P=0.044$).

Discussion

Glutamine is the most abundant amino acid in the body. A tumor may act as a gln trap by depleting host gln stores and resulting in cachexia. This fact led to the development of one of the first successful metabolic therapies, L-asparaginase, for the treatment of acute lymphoblastic leukemia (ALL) 30 years ago. L-asparaginase is able to deplete plasma asparagine and gln, while ALL cells, which require large amounts of gln, are affected by this treatment (18). However, L-asparaginase has only been proven to be effective in ALL and certain natural killer/T-cell lymphomas, with no effect in acute myeloid leukemia, non-Hodgkin's lymphoma and solid tumors (19). Recent studies eventually provided evidence that explained this lack of antitumor effect of gln deprivation, by suggesting that various tumor types may reside in an environment where gln is profoundly limited and they adapted to this by pursuing strategies in order to sustain their growth and survival (20-22). In most glutamine-deprived cell lines, induction of *de novo* biosynthesis of gln or acquisition of gln through catabolism of extracellular and intracellular proteins has been indicated to provide a source of missing gln for cells (23).

The variation of nutrient acquisition in amino acid-replete and amino acid-starved settings varies among different cancer types. For instance, the response of human breast carcinoma cells to gln deprivation was observed to exert the same effects as lactate accumulation in tumors: Increased NF- κ B activity and subsequent stimulation of IL-8/C-X-C motif chemokine ligand 8 expression, which, in turn, promotes angiogenesis (24). In a recent study, gln supplementation in a rat model blocked melanoma tumor growth by suppressing epigenetically activated oncogenic pathways (25). These contradictory results from *in vitro*, animal and clinical studies clearly indicate that reliable information about the effects of supplemental gln may only be obtained based on *in vivo* studies for each cancer type

Table VI. Use of opioids according to demographics and clinical characteristics.

Item	Opioids		P-value
	No	Yes	
Age, years	64.9±10.6	66.3±12.4	0.621 ^a
Sex			0.532 ^b
Male	34 (64.2)	19 (35.8)	
Female	13 (72.2)	5 (27.8)	
PS			0.153 ^b
0	22 (75.9)	7 (24.1)	
1/2	25 (59.5)	17 (40.5)	
Cancer type			0.278 ^b
Chest tumor	24 (72.7)	9 (27.3)	
Head & neck	23 (60.5)	15 (39.5)	
Grade			0.951 ^b
1/2	19 (61.3)	12 (38.7)	
3	18 (62.1)	11 (37.9)	
Stage			0.134 ^b
I/II	17 (77.3)	5 (22.7)	
III/IV	27 (58.7)	19 (41.3)	
Duration of RT, days	36.2±12.3	28.6±13.1	0.023 ^a
Total dose, cGY	5,511.1±1,123.4	5,447.1±1,351.9	0.833 ^a
Irradiation fractions	26.6±6.8	26.2±7.8	0.847 ^a
Length of the radiated esophagus from treatment planning, cm	11.8±2.9	13.6±3.6	0.024 ^a
Length of the radiated esophagus from treatment planning (cm)			0.018 ^b
<12	24 (77.4)	7 (22.6)	
>12	23 (57.5)	17 (42.5)	
Prior surgery			0.317 ^b
No	33 (70.2)	14 (29.8)	
Yes	14 (58.3)	10 (41.7)	
Prior chemotherapy			0.442 ^b
No	28 (70)	12 (30)	
Yes	19 (61.3)	12 (38.7)	
Concurrent chemotherapy			0.652 ^b
No	30 (68.2)	14 (31.8)	
Yes	17 (63)	10 (37)	
Only RT			0.272 ^b
No	27 (61.4)	17 (38.6)	
Yes	20 (74.1)	7 (25.9)	
Subsequent chemotherapy			0.957 ^b
No	33 (66)	17 (34)	
Yes	14 (66.7)	7 (33.3)	

^aStudent's t-test; ^bPearson's χ^2 test. Values are expressed as n (%) or the mean ± standard deviation. PS, performance status; RT, radiotherapy.

separately (26). Particularly for solid tumors, supplementation of gln was indicated to decrease tumor growth through stimulation of the immune system and protection of mucosal integrity (27).

Treatment for H&NT primarily involves three modalities: Surgery, RT and CT, administered alone or in combination. RT alone is the most common treatment for certain types of H&NT, such as cancer of the nasopharynx, larynx and

Table VII. Use of opioids according to the presence of adverse events.

Item	Opioids		P-value
	No	Yes	
Stomatitis, grade			0.001 ^a
0/1	40 (87.0)	11 (50.0)	
2/3	6 (13.0)	11 (50.0)	
Esophagitis, grade			0.075 ^a
0/1	22 (46.8)	6 (25.0)	
2/3	25 (53.2)	18 (75.0)	
Dysphagia, grade			0.623 ^a
0/1	22 (47.8)	10 (41.7)	
2/3	24 (52.2)	14 (58.3)	
Pain, grade			0.005 ^a
0/1	40 (85.1)	13 (54.2)	
2/3	7 (14.9)	11 (45.8)	
Mycosis			0.103 ^a
No	31 (66.0)	11 (45.8)	
Yes	16 (34.0)	13 (54.2)	
At least one adverse event			0.412 ^b
No	6 (13.3)	1 (4.5)	
Yes	39 (86.7)	21 (95.5)	

^aPearson's χ^2 test; ^bFisher's exact test. Values are expressed as n (%).

oropharynx (28). The therapeutic strategies employed for resectable stage III non-small cell LC (NSCLC) include surgical resection with adjuvant CT and sequential RT, preoperative CT with adjuvant RT, preoperative CT and RT. In most patients with stage III NSCLC, the tumors are unresectable and are treated with CT and RT therapy, frequently referred to as combined modality therapy or concurrent CT-RT. For stage IV NSCLC, treatment is based on systematic CT + palliative RT (29). In the present study, patients were treated with sequential or concurrent CT-RT (38%) or RT alone (38%) classified as stage III in the majority of subjects (53.6%).

According to the literature, gln doses of up to 40 g/day via total parenteral nutrition and up to 30 g/day taken orally in divided doses were determined to be a safe and effective treatment for mucositis and stomatitis (7). All study patients received oral gln supplementation (15 g bid) and no gln intolerance or toxicity was reported.

In H&NT patients on RT, oral gln was applied as a 'swish and swallow' therapy with the purpose to increase enterocyte contact and decrease the severity and duration

of stomatitis. This rationale implies that not only the dose, but also effective penetration and local mucosal cell uptake of glutamine are probably important (13). In the published studies, different gln supplementation regimens were implemented, from the first round of conventional CT and/or RT until two weeks post-therapy, with positive results indicating either a shorter duration or reduced severity of OM (30-39).

For patients with chest tumors and LC, as far as esophagitis is concerned, the same beneficial results were indicated in most studies (40-44). First, a pilot study by Algara *et al* (40) assessed the usefulness of oral gln to prevent RT-CT-induced esophagitis, along with a dosimetric parameter of V50 predictive of esophagitis and its duration. The randomized trials that followed (41,42) evaluated the efficacy of oral gln in the prevention of acute RT-induced esophagitis (ARIE) and weight loss in patients with LC. In a study by Topkan *et al* (41), V55, the mean volume of the lung receiving 55 Gy, was the only dosimetric parameter correlated with the severity of ARIE in gln-free patients and it was concluded that gln may be beneficial in the prevention of ARIE and weight loss in patients with LC undergoing thoracic irradiation.

According to the results of the present study, the adverse event of stomatitis grade 2 to 3 was significantly associated with the cancer type; it was observed more frequently in patients with H&NT ($P=0.001$), and with modality treatment; previous surgery ($P<0.001$) and concurrent CT ($P=0.044$). Concerning the adverse events of esophagitis and dysphagia, both were significantly associated with concurrent CT-RT ($P=0.020$ and $P=0.008$, respectively).

Published data so far regarding gln supplementation focused on depicting the decrease in the incidence and/or severity of standard of care treatment-associated toxicities in tumors of the lung and esophagus, as well as H&NT (13,15). For the first time, to the best of our knowledge, the present study determined a dosimetric parameter, such as the irradiated esophagus length from treatment planning, to be correlated with analgesic therapy and weight loss. In patients who used opioids, the mean length of the irradiated esophagus from treatment planning ($P=0.024$) and duration of RT ($P=0.023$) were significantly greater. In addition, the use of opioids was more frequent in cases where the length of the irradiated esophagus from treatment planning was >12 cm ($P=0.018$). For weight loss after RT, there was also significant association with duration of RT ($P=0.001$), total dose cGY ($P<0.001$), irradiation fractions ($P<0.001$) and length of irradiated esophagus from treatment planning ($P=0.009$) and concurrent or subsequent CT ($P=0.007$ and $P=0.041$, respectively). The key findings and features of the present study are summarized in Fig. 2.

The present study was not without limitations. For example, all patients received the same dose of oral gln, and no comparison to a control group (taking no gln), was made. Thus, further case-control studies with larger sample sizes are required to validate the results presented here.

In conclusion, the use of oral gln supplementation may have an important role in reducing acute radiation toxicities, weight loss and the need for analgesics in patients with T&UAM, mainly if the treatment plan includes CT and RT. Most of the clinical trials evaluating the use of oral gln in chest and H&N tumors had positive results regarding its protective effect

Table VIII. Weight loss after RT according to demographics and clinical characteristics.

Item	Weight loss after RT		P-value
	No	Yes	
Age, years	66.2±11.6	64.8±10.9	0.613 ^a
Sex			0.441 ^b
Male	21 (39.6)	32 (60.4)	
Female	9 (50.0)	9 (50.0)	
PS			0.393 ^b
0	14 (48.3)	15 (51.7)	
1/2	16 (38.1)	26 (61.9)	
Cancer type			0.051 ^b
Chest tumor	18 (54.5)	15 (45.5)	
Head & neck	12 (31.6)	26 (68.4)	
Grade			0.058 ^b
1/2	16 (51.6)	15 (48.4)	
3	8 (27.6)	21 (72.4)	
Stage			0.697 ^b
I/II	8 (36.4)	14 (63.6)	
III/IV	19 (41.3)	27 (58.7)	
Duration of RT, days	27.6±13.3	37.7±11.3	0.001 ^a
Total dose, cGY	4,919.7±1,324.7	5,906.3±900.0	<0.001 ^a
Irradiation fractions	23.0±7.8	28.9±5.3	<0.001 ^a
Length of the radiated esophagus from treatment planning, cm	11.3±2.3	13.3±3.6	0.009 ^a
Length of the radiated esophagus from treatment planning, cm			0.059 ^b
<12	17 (54.8)	14 (45.2)	
>12	13 (32.5)	27 (67.5)	
Prior surgery			0.663 ^b
No	19 (40.4)	28 (59.6)	
Yes	11 (45.8)	13 (54.2)	
Prior chemotherapy			0.160 ^b
No	14 (35.0)	26 (65.0)	
Yes	16 (51.6)	15 (48.4)	
Concurrent chemotherapy			0.007 ^b
No	24 (54.5)	20 (45.5)	
Yes	6 (22.2)	21 (77.8)	
Only RT			0.431 ^b
No	17 (38.6)	27 (61.4)	
Yes	13 (48.1)	14 (51.9)	
Subsequent chemotherapy			0.041 ^b
No	25 (50.0)	25 (50.0)	
Yes	5 (23.8)	16 (76.2)	

^aStudent's t-test; ^bPearson's χ^2 test. Values are expressed as n (%) or the mean ± standard deviation. PS, performance status; RT, radiotherapy.

on the mucositis, esophagitis and weight loss level (30-44). The favorable efficacy and low toxicity of oral gln observed

in clinical trials provide a strong rationale for large RCTs in patients with cancer receiving RT and/or CT (45,46). Recent

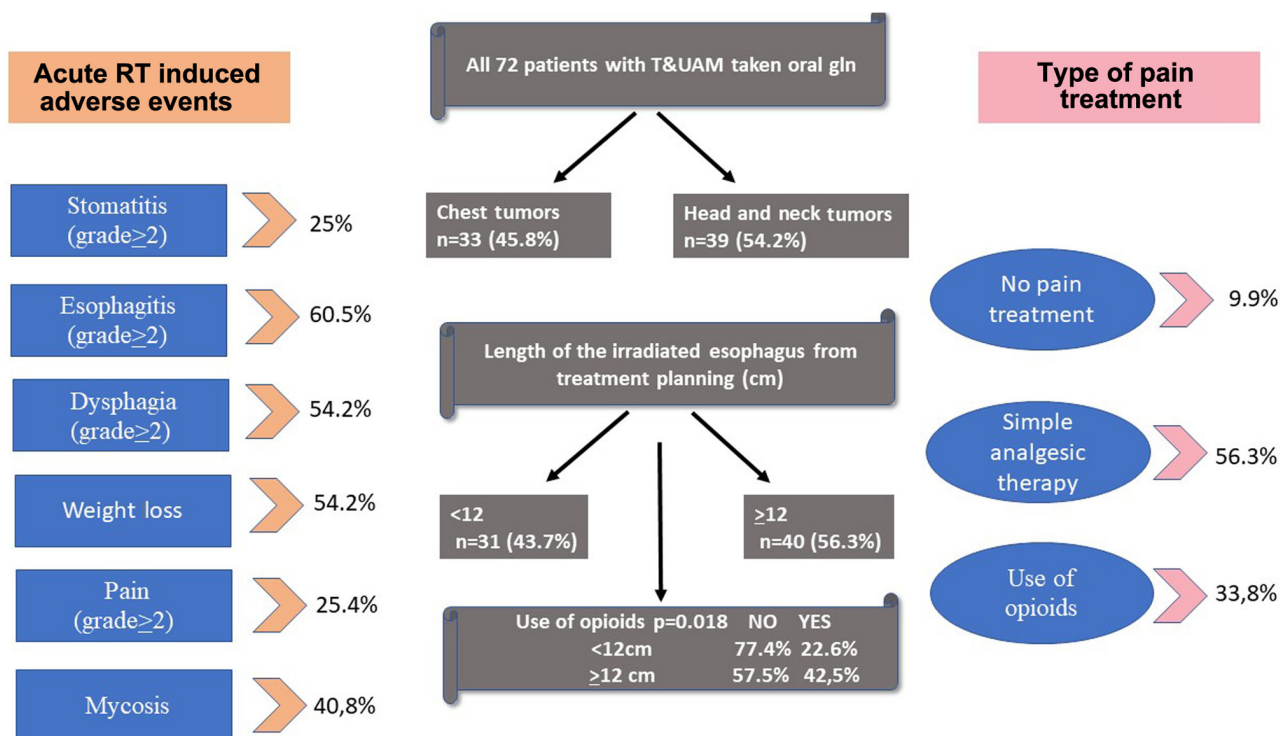


Figure 2. Acute RT-induced adverse events and type of treatment. Percentages of acute adverse events in 72 patients with T&UAM who took oral gln powder at doses of 15 g 2 times per day for the total duration of radiation treatment. T&UAM, thoracic and upper aerodigestive malignancies; RT, radiotherapy; gln, glutamine.

meta-analyses specifically focusing on OM in such groups of patients concluded that gln reduces the severity of OM and the incidence of severe OM (grade 3 and 4) (47,48). In addition, gln reduced the incidence of opioid analgesic use, feeding tube use, hospitalization and treatment interruption caused by OM (46).

The present study revealed dosimetric parameters, including the total RT dose, the irradiated esophagus length, the concurrent CT regimen and the radiation techniques applied, which influenced the incidence and severity of RT toxicities. Further RCTs will help comprehensively analyze precise dosimetric parameters from RT treatment planning, and indicate the group of patients most likely to benefit from gln supplementation. In addition, RCTs will help identify the appropriate individualized dose and duration of treatment for gln supplementation according to the specific cancer type and the applied therapeutic modality in order to optimize its protective effect, to reduce the severity and duration of RT toxicities, relieving the degree of mucosal pain.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LV and NS contributed to the conception and design of the study. ND supervised the study. ND and LV confirm the authenticity of all the raw data. AP was involved in the patients' clinical history and data acquisition and wrote the manuscript. LV was involved in the patient recruitment process and in the collection of the subjects' medical files and their evaluation. AP and MP analyzed the data. ND, AC, DAS, GL and SK reviewed and edited the manuscript, and contributed to the interpretation of the data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Athens Medical Center (Athens, Greece; approval no. 2281/26-04-2013) and written informed consent was provided by all participants prior to the study start.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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