

# Evaluation of the relationship between serum ghrelin levels and cancer cachexia in patients with locally advanced nonsmall-cell lung cancer treated with chemoradiotherapy

## ABSTRACT

**Background:** Ghrelin plays a role in mechanisms related to cancer progression – including cell proliferation, invasion and migration, and resistance to apoptosis in the cell lines from several cancers. We investigated the role of ghrelin levels in cancer cachexia-anorexia in patients with locally advanced nonsmall-cell lung cancer (NSCLC) treated with chemoradiotherapy (CRT).

**Materials and Methods:** This study involved 84 NSCLC patients who had received concomitant CRT. Blood ghrelin levels were compared before and 3 months after CRT. Meanwhile, changes in body weight of the patients were also investigated with changes in ghrelin levels before and after CRT.

**Results:** Ghrelin levels were significantly decreased in line with changes in patients' weights in patients receiving CRT ( $P < 0.001$ ). Serum albumin levels and inflammatory-nutritional index were significantly decreased after radiotherapy (RT) ( $3.01 \pm 0.40$  g/dL,  $0.38 \pm 0.20$ ) when compared with its baseline levels ( $3.40 \pm 0.55$  g/dL,  $0.86 \pm 0.71$ ,  $P < 0.001$ , respectively). Serum C-reactive protein levels were significantly increased after CRT ( $7.49 \pm 6.53$  mg/L) when compared with its baseline levels ( $9.54 \pm 3.80$  mg/L,  $P = 0.038$ ). After RT, ghrelin levels in patients were positively correlated with body mass index ( $r = 0.830$ ,  $P < 0.001$ ) and albumin ( $r = 0.758$ ,  $P < 0.001$ ).

**Conclusion:** Ghrelin may play a role in the pathogenesis of weight loss in NSCLC patients. Ghrelin seems to be implicated in cancer-related weight loss. Ghrelin, cancer, and RT all together have a role in tumor-related anorexia-cachexia in patients with NSCLC. Results of this study need further evaluation as regards to its potential role as an adjuvant diagnostic or prognostic marker.

**KEY WORDS:** Cancer cachexia, chemoradiotherapy, ghrelin, locally advanced nonsmall cell lung cancer

## INTRODUCTION

Lung cancer is the most common cancer in all over the world and cancer-related death in both sexes.<sup>[1]</sup> Lung cancer is classified as small-cell lung cancer (SCLC) and non-SCLC (NSCLC) in terms of treatment and prognosis. NSCLC is responsible for 80%–85% of all cases.<sup>[2]</sup> Other factors that determine the prognosis of the disease are the stage of the tumor, gender, age, and weight loss.<sup>[3]</sup> Anorexia and cachexia due to tumor characteristics affect patients' mortality, morbidity, and quality of life. In the course of life-threatening diseases such as cancer, more than 6% weight loss accompanied by hypercatabolic condition in the last 6 months is defined as cachexia.

Lung cancer and gastrointestinal system (GIS) cancers are two types of tumors which are the most common causes of cancer cachexia.<sup>[4]</sup> Cancer cachexia which is one of the most frequent effects of malignancies may be responsible for more than 20% of cancer-related deaths and is associated with poor prognosis. Cancer cachexia is a complex, multifactorial metabolic condition involving weight loss and anorexia secondary to increased skeletal

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow\_reprints@wolterskluwer.com

**Cite this article as:** Uysal P, Afsar CU, Sozer V, Inanc B, Agaoglu F, Gural Z, *et al.* Evaluation of the relationship between serum ghrelin levels and cancer cachexia in patients with locally advanced nonsmall-cell lung cancer treated with chemoradiotherapy. *J Can Res Ther* 2020;16:855-9.

Pelin Uysal,  
Cigdem Usul  
Afsar<sup>1</sup>,  
Volkan Sozer<sup>2</sup>,  
Berrin Inanc<sup>3</sup>,  
Fulya Agaoglu,  
Zeynep Gural,  
Nevin Yaman  
Fazlolu<sup>4</sup>,  
Caglar  
Cuhadaroglu<sup>5</sup>,  
Hafize Uzun<sup>6</sup>

Department of Chest Diseases, Faculty of Medicine, Atakent Hospital, Mehmet Ali Aydınlar University, <sup>1</sup>Department of Medical Oncology, Faculty of Medicine, Bakırköy Hospital, Mehmet Ali Aydınlar University, <sup>2</sup>Department of Biochemistry, Yıldız Technical University, <sup>3</sup>Department of Radiation Oncology, İstanbul Education and Research Hospital, <sup>5</sup>Department of Chest Diseases, Faculty of Medicine, Altunizade Hospital, Mehmet Ali Aydınlar University, <sup>6</sup>Department of Biochemistry, Cerrahpaşa Faculty of Medicine, İstanbul University-Cerrahpaşa, İstanbul, <sup>4</sup>Department of Chest Diseases, Faculty of Medicine, Tekirdağ Namık Kemal University, Tekirdağ, Turkey

Submitted: 03-Jan-2019

Revised: 23-May-2019

Accepted: 22-Aug-2019

Published: 16-May-2020

Access this article online

Website: [www.cancerjournal.net](http://www.cancerjournal.net)

DOI: 10.4103/jcrt.JCRT\_10\_19

Quick Response Code:



**For correspondence:**

Prof. Hafize Uzun,

Department of Biochemistry, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, 34303 Cerrahpasa, Istanbul, Turkey.

E-mail: huzun59@hotmail.com

muscle and fat loss.<sup>[5]</sup> The development of cachexia in a patient with cancer decreases the tolerance to treatment, consumes hope due to depressive mood, and decreases treatment response. Negative effects on treatment response and decrease in survival lead to deterioration of quality of life.

Ghrelin is a hormone which is called endogenous growth hormone-associated peptide, is released from the gastric mucosa, and has roles in regulating energy balance and nutrient uptake because it has a strong growth hormone-releasing effect independent of hypothalamus.<sup>[6,7]</sup> Ghrelin levels are found to be increased in cachexia and anorexia but decreased in obesity.<sup>[8]</sup> In literature, there are studies investigating the relationship between blood ghrelin levels and tumor cachexia in cancer patients.<sup>[9,10]</sup> However, the number of studies performed in patients with lung cancer treated with chemoradiotherapy (CRT) is almost negligible. It is a known fact that tolerability of radiotherapy (RT) is difficult in these patients. In some studies, it has been reported that plasma ghrelin levels are increased and ghrelin levels are positively correlated with tumor necrosis factor- $\alpha$  and negatively correlated with body mass index (BMI) in patients with lung cancer and congestive heart failure.<sup>[11,12]</sup> Anamorelin (ghrelin analog) has been used in oncology to treat cachexia in some types of tumors.<sup>[13-15]</sup>

We planned this study to investigate the role of ghrelin levels in cancer cachexia-anorexia in patients with locally advanced NSCLC treated with CRT.

**MATERIALS AND METHODS**

The study was designed prospectively. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study was approved by the Ethics Committee of Mehmet Ali Aydınlar University Medical Faculty, and written informed consent was obtained from each patient (ATADEK-2017/14). Detailed history was taken from all participants and physical examinations were performed.

The serum samples of the lung cancer patients who were referred to Acibadem Mehmet Ali Aydınlar University Medical Faculty, Department of Medical Oncology and Radiation Oncology, from May 2018 to November 2018 were obtained. All patients had histologically confirmed lung cancer diagnosis and had not received chemotherapy (CTx) or CRT within

6 months. The staging was determined according to the American Joint Committee on Cancer and International Union against Cancer staging systems. Stage IIIA and IIIB patients were included in the study, and all had taken curative CRT. Patients with morbid obesity, who had another malignancy, and who had surgery within 6 months were excluded.

The pretreatment evaluation included assessment of detailed clinical history and physical examination with a series of biochemistry tests. Those with Eastern Cooperative Oncology Group performance status 1 or less and appropriate blood chemistry tests received CTx which included different combinations of paclitaxel, cisplatin, carboplatin, vinblastine, etoposide, and pemetrexed with concurrent RT. The most commonly given dose for definitive RT was 60–70 Gy in 2 Gy fractions. Response to treatment was determined according to the revised RECIST criteria<sup>[16]</sup> version 1.1 by the investigators and classified as follows: complete response, partial response (PR), stable disease (SD), or progressive disease (PD). Follow-up programs of lung cancer patients consisted of clinical, laboratory, and imaging techniques such as computed tomography (CT) scan or positron emission tomography/CT depending on which imaging methods were used at baseline and performed at 12-week intervals. Patients with either PR or SD were classified as responders, and patients with PD were considered as nonresponders.

**Laboratory analysis***Sample collection and preparation*

For all persons, clinical parameters including routine biochemical parameters were measured using the standard protocols. Blood samples taken from patients were collected in ethylenediaminetetraacetic acid-containing tubes and in dry tubes without anticoagulants. Blood samples were taken in tubes after overnight fasting before RT, in the 5<sup>th</sup> week of RT (acute effects of RT were observed), and at 3 months after RT to investigate the chronic effects of RT. Serum and plasma parts were separated immediately and stored at  $-80^{\circ}\text{C}$  until analysis.

Routine biochemical parameters were measured by the autoanalyzer (Hitachi Modular System, Roche Diagnostic, USA). Serum C-reactive protein (CRP) levels were measured by a nephelometric method (Immage 800 Beckman Coulter). Complete blood count parameters were obtained with automatic hematology analyzer (Siemens-Sysmex, Germany).

Inflammatory-nutritional index (INI) in patients was conducted to the laboratory for the measurement of serum albumin and CRP and subsequent calculation of the INI.<sup>[17]</sup>

### Measurement of plasma ghrelin (total) levels

Plasma ghrelin levels were measured by a commercially available competitive enzyme-linked immunoassay kit (Enzyme-Linked Immunosorbent Assay, Organon Teknika, Durham NC, USA). The coefficients of intra- and inter-assay variation were 5.1% ( $n = 20$ ) and 6.0% ( $n = 20$ ), respectively.

### Statistical analysis

Statistical analysis was performed using the SPSS 20.0 (SPSS Inc., Chicago, IL, USA). All data were first checked for normality. Normally distributed continuous variables were presented as mean  $\pm$  standard deviation and analyzed by one-way analysis of variance followed by Tukey's multiple comparison tests. The paired-sample *t*-tests were used to compare the means before and after CTx, in a single group of patients. Pearson's and Spearman's correlations were used for numerical and nominal data, respectively. Differences were considered statistically significant when the  $P < 0.05$ .

## RESULTS

Characteristics of the 84 patients included NSCLC are shown in Table 1. Patients' stages were as follows; Stage IIIA (36%) and Stage IIIB (64%). Squamous histology was 41%, adenocarcinoma was 45%, and other was 14%. CTx and RT were given concurrently to 84 patients (100%), of whom 46 (55%) received cisplatin-based CTx and 38 (45%) received carboplatin-based CTx. Concurrent CT regimens were cisplatin 50 mg/m<sup>2</sup> on days 1, 8, 29, and 36 with etoposide 50 mg/m<sup>2</sup> on days 1–5 and 29–33; paclitaxel 50 mg/m<sup>2</sup> weekly with carboplatin AUC2 and for nonsquamous tumors only cisplatin 75 mg/m<sup>2</sup> on day 1 with pemetrexed 500 mg/m<sup>2</sup> on day 1 every 21 days for three cycles. All patients ( $n = 84$ ; 100%) received a total radiation dose of at least 60 Gy (range 50–66 Gy) in 2.0 Gy daily fractions.

Blood biochemical changes before and 3 months after CRT in patients with locally advanced NSCLC are shown in Table 2. Ghrelin levels ( $42.90 \pm 10.55$ ) after completion of CRT were lower than baseline ghrelin levels ( $63.10 \pm 10.22$ ) before the start of CRT in patients with locally advanced NSCLC. Neutrophil levels were not found to be significantly different between pre-CRT and 3 months after CRT. Serum albumin and INI levels were significantly decreased in after RT ( $3.01 \pm 0.40$  g/dL,  $0.38 \pm 0.20$ ) when compared with its baseline levels ( $3.40 \pm 0.55$  g/dL,  $P < 0.001$ ;  $0.86 \pm 0.71$ ,  $P < 0.001$ , respectively). Serum CRP levels were significantly increased in after CRT ( $7.49 \pm 6.53$  mg/L) when compared with its baseline levels ( $9.54 \pm 3.80$  mg/L,  $P = 0.038$ ).

After CRT, ghrelin levels in patients were positively correlated with BMI ( $r = 0.830$ ,  $P < 0.001$ ) and albumin ( $r = 0.758$ ,  $P < 0.001$ ). After CRT, ghrelin levels were positively correlated with INI ( $r = 0.408$ ,  $P < 0.001$ ) and weak negatively correlated with CRP (for each comparison ( $r = 0.244$ ,  $P < 0.01$ ). Ghrelin levels were negatively correlated with the extent of weight changes ( $r = -0.33$ ,  $P < 0.01$ ).

**Table 1: General characteristics and treatment modalities of nonsmall-cell lung cancer patients**

Characteristic	n (%)
Total number of patients	84
Median age (years)	65 (48-84)
Gender	
Female	66 (79)
Male	18 (21)
PS	
0	46 (55)
1	34 (41)
2	4 (4)
Clinical stage	
IIIA	54 (64)
IIIB	30 (36)
Histopathology	
Adenocarcinoma	34 (41)
SqCC	38 (45)
Other	12 (14)

PS=Performance status, SqCC=Squamous cell carcinoma

**Table 2: Blood tests changes in preradiotherapy and 3 months after radiotherapy in nonsmall-cell lung cancer patients (n=84)**

	Before CRT	3 months after CRT	P
Weight (kg)	72.05 $\pm$ 12.32	67.62 $\pm$ 11.84	<0.001
BMI (kg/m <sup>2</sup> )	26.18 $\pm$ 4.05	24.60 $\pm$ 3.82	<0.001
Percentage EBWL		6.13 $\pm$ 3.96	-
WBC ( $\times 10^3/\mu$ L)	10.20 $\pm$ 5.04	6.14 $\pm$ 3.17	<0.001
Neutrophil ( $\times 10^9/L$ )	7.51 $\pm$ 4.74	6.52 $\pm$ 12.69	NS
Lymphocyte ( $\times 10^9/L$ )	1.65 $\pm$ 0.87	0.77 $\pm$ 0.47	<0.001
PLT ( $\times 10^3/\mu$ L)	307 $\pm$ 134	237 $\pm$ 104	0.001
Albumin (g/dL)	3.40 $\pm$ 0.55	3.01 $\pm$ 0.40	<0.001
CRP (mg/L)	7.49 $\pm$ 6.53	9.54 $\pm$ 3.80	0.038
INI	0.86 $\pm$ 0.71	0.38 $\pm$ 0.20	<0.001
Ghrelin (pg/mL)	63.10 $\pm$ 10.22	42.90 $\pm$ 10.55	<0.001

BMI=Body mass index, EBWL=Excess body weight loss, WBC=White blood count, PLT=Platelet, CRP=C-reactive protein, INI=Inflammatory-nutritional index, NS=Not available, CRT=Chemoradiotherapy

## DISCUSSION

Lung cancer is the most frequent cause of cancer-related deaths worldwide. Cancer cachexia is a multilayered syndrome which is a result of interaction between tumor cells and the host.<sup>[18]</sup> Different cellular and soluble mediators are activated as a result of this interaction, and they trigger many metabolic and nutritional alterations.<sup>[18]</sup>

Ghrelin has been characterized as a ligand of the growth hormone secretagogue receptor (GHSR), and it is a multifunctional peptide and plays a role in the regulation of energy balance, gastric acid release, appetite, insulin secretion, gastric motility, and the turnover of gastric and intestinal mucosa.<sup>[19]</sup> Cancer is a multiplex disease in which different and many pathways are activated. Several critical factors are involved in cancer including proliferation, apoptosis, metastasis, angiogenesis, and drug resistance.<sup>[19]</sup>

Although there is growing evidence that indicates the function of ghrelin in regulating a number of processes related to cancer progression, its primary role is not understood yet.

Many cancer studies have observed expression of ghrelin and its receptor (GHSR1a, 1b, or both) in renal cell carcinoma, pancreatic cancer, breast cancer, gonadal cancer, gastric cancer, colorectal cancer, prostate cancer, thyroid cancer, lung cancer, ovarian cancer, and oral cancer.<sup>[20-24]</sup> Ghrelin promotes growth of adipose tissue by activation of lipogenic pathways and can influence regulation of skeletal muscle mass by stimulation of insulin-like growth factor 1 production.<sup>[25]</sup>

Ghrelin levels after completion of CRT were lower than baseline ghrelin levels before the start of CRT in patients with locally advanced NSCLC. Ghrelin has a protective factor against the toxic effects of chemotherapeutic agents. Therefore, ghrelin levels may be reduced. If we investigate the relationship between ghrelin and lung cancer, it has been found that ghrelin promotes human NSCLC cell proliferation through PI3K/Akt/mTOR/P70S6K and ERK signaling pathways.<sup>[26]</sup> Anamorelin (a ghrelin analog) is found to be an important molecule which significantly increases lean body mass, and it is studied in patients with advanced NSCLC.<sup>[27,28]</sup>

Although there is evidence of anorexia and ghrelin relationship in literature, there are only limited data about RT effect, cancer anorexia-cachexia, and ghrelin relationship. For head and neck carcinomas, ghrelin is found to be an important peptide for the prevention of radiation-induced oral mucositis.<sup>[29-31]</sup> Other cancer which is explored for ghrelin, appetite, and RT interaction is gastrointestinal cancer. In one study, it has been found that initiation of ghrelin analog in patients receiving CRT with GIS malignancies can both prevent weight loss by increasing appetite and decrease severity of inflammation.<sup>[9]</sup>

Serum albumin level is commonly used to assess nutritional status. Malnutrition is related with hypoalbuminemia, and both are common in patients with NSCLC.<sup>[32]</sup> In the current study, serum albumin levels after RT were lower than the baseline albumin levels before the initiation of therapy in patients with NSCLC. Albumin levels were related to the development of RT-induced toxicity. Arrieta *et al.*<sup>[33]</sup> showed that CTx-induced toxicity in NSCLC patients treated with paclitaxel and cisplatin was associated with malnutrition and hypoalbuminemia. Wang *et al.*<sup>[34]</sup> suggested that improvement and early assessment of the serum albumin level in patients with inoperable NSCLC may be beneficial effects after CTx. In the present study, ghrelin levels in patients with NSCLC were positively correlated with albumin. Our and other studies<sup>[33-34]</sup> showed that early nutritional assessment and support treatment might confer beneficial effects.

Systemic inflammation, which plays an important role in cachexia genesis and progression, should be evaluated, considering that it implies worsening in prognosis.<sup>[34,35]</sup> Ghrelin levels in patients with NSCLC were positively correlated with INI in the current study. The present study showed that risk INI is a simple scoring system based on routine, cheap, and easily available laboratory tests.

In our study, we found that ghrelin levels decrease during CRT in lung cancer patients who have a positive correlation with the decrease of patients' weights and albumin levels. Cancer cachexia is closely linked to patients with NSCLC. RT is an inflammatory process which can decrease the appetite of patients and results in weight loss and cachexia. Ghrelin, cancer, and RT all together have a role in tumor-related anorexia-cachexia. There are many effects in the body as anabolic effects of ghrelin but need further investigation. This is an interesting finding, and it should be lightened with other studies.

## CONCLUSION

Ghrelin may play a role in the pathogenesis of weight loss in NSCLC patients. Ghrelin, cancer, and RT all together have a role in tumor-related anorexia-cachexia in patients with NSCLC. Results of this study need further evaluation as regards to its potential role as an adjuvant diagnostic or prognostic marker.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87-108.
2. World Health Organization. International Agency for Research on Cancer, Section of Cancer Information. *Cancer Incidence and Mortality Worldwide*. Geneva: World Health Organization; 2008.
3. Ademuyiwa FO, Johnson CS, White AS, Breen TE, Harvey J, Neubauer M, *et al.* Prognostic factors in stage III non-small-cell lung cancer. *Clin Lung Cancer* 2007;8:478-82.
4. Fortunati N, Manti R, Birocco N, Pugliese M, Brignardello E, Ciuffreda L, *et al.* Pro-inflammatory cytokines and oxidative stress/antioxidant parameters characterize the bio-humoral profile of early cachexia in lung cancer patients. *Oncol Rep* 2007;18:1521-7.
5. Lasheen W, Walsh D. The cancer anorexia-cachexia syndrome: myth or reality? *Support Care Cancer* 2009;9:772-6.
6. Itoh T, Nagaya N, Yoshikawa M, Fukuoka A, Takenaka H, Shimizu Y, *et al.* Elevated plasma ghrelin level in underweight patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:879-82.
7. Müller TD, Nogueiras R, Andermann ML, Andrews ZB, Anker SD, Argente J. Ghrelin. *Mol Metab* 2015;4:437-60.
8. Marzullo P, Verti B, Savia G, Walker GE, Guzzaloni G, Tagliaferri M, *et al.* The relationship between active ghrelin levels and human obesity involves alterations in resting energy expenditure. *J Clin Endocrinol Metab* 2004;89:936-9.
9. Karaca F, Afsar CU, Gunaldi M, Erkurt E, Ercolak V, Sertdemir Y, *et al.* Alterations of ghrelin with weights and correlation among ghrelin, cytokine and survival in patients receiving chemoradiotherapy for gastrointestinal cancers. *Int J Clin Exp Med* 2015;8:876-82.
10. Karapanagiotou EM, Polyzos A, Dilana KD, Gratsias I, Boura P, Gkiozos I, *et al.* Increased serum levels of ghrelin at diagnosis mediate body weight loss in non-small cell lung cancer (NSCLC) patients. *Lung Cancer* 2009;66:393-8.
11. Shimizu Y, Nagaya N, Isobe T, Imazu M, Okumura H, Hosoda H, *et al.*

- Increased plasma ghrelin level in lung cancer cachexia. *Clin Cancer Res* 2003;9:774-8.
12. Nagaya N, Uematsu M, Kojima M, Date Y, Nakazato M, Okumura H, *et al.* Elevated circulating level of ghrelin in cachexia associated with chronic heart failure: Relationships between ghrelin and anabolic/catabolic factors. *Circulation* 2001;104:2034-8.
  13. Zhang H, Garcia JM. Anamorelin hydrochloride for the treatment of cancer-anorexia-cachexia in NSCLC. *Expert Opin Pharmacother* 2015;16:1245-53.
  14. Currow DC, Abernethy AP. Anamorelin hydrochloride in the treatment of cancer anorexia-cachexia syndrome. *Future Oncol* 2014;10:789-802.
  15. Argilés JM, Stemmler B. The potential of ghrelin in the treatment of cancer cachexia. *Expert Opin Biol Ther* 2013;13:67-76.
  16. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47.
  17. Alberici Pastore C, Paiva Orlandi S, González MC. Association between an inflammatory-nutritional index and nutritional status in cancer patients. *Nutr Hosp* 2013;28:188-93.
  18. Currow DC, Maddocks M, Cella D, Muscaritoli M. Efficacy of anamorelin, a novel non-peptide ghrelin analogue, in patients with advanced non-small cell lung cancer (NSCLC) and cachexia-review and expert opinion. *Int J Mol Sci* 2018;19. pii: E3471.
  19. Lin TC, Hsiao M. Ghrelin and cancer progression. *Biochim Biophys Acta Rev Cancer* 2017;1868:51-7.
  20. Korbonits M, Bustin SA, Kojima M, Jordan S, Adams EF, Lowe DG, *et al.* The expression of the growth hormone secretagogue receptor ligand ghrelin in normal and abnormal human pituitary and other neuroendocrine tumors. *J Clin Endocrinol Metab* 2001;86:881-7.
  21. Lin TC, Liu YP, Chan YC, Su CY, Lin YF, Hsu SL, *et al.* Ghrelin promotes renal cell carcinoma metastasis via snail activation and is associated with poor prognosis. *J Pathol* 2015;237:50-61.
  22. Volante M, Allia E, Fulcheri E, Cassoni P, Ghigo E, Muccioli G, *et al.* Ghrelin in fetal thyroid and follicular tumors and cell lines: Expression and effects on tumor growth. *Am J Pathol* 2003;162:645-54.
  23. Nikolopoulos D, Theocharis S, Kouraklis G. Ghrelin's role on gastrointestinal tract cancer. *Surg Oncol* 2010;19:e2-e10.
  24. Cassoni P, Papotti M, Ghè C, Catapano F, Sapino A, Graziani A, *et al.* Identification, characterization, and biological activity of specific receptors for natural (ghrelin) and synthetic growth hormone secretagogues and analogs in human breast carcinomas and cell lines. *J Clin Endocrinol Metab* 2001;86:1738-45.
  25. Malik JS, Yennurajalingam S. Prokinetics and ghrelin for the management of cancer cachexia syndrome. *Ann Palliat Med* 2019;8:80-5.
  26. Zhu J, Yao J, Huang R, Wang Y, Jia M, Huang Y. Ghrelin promotes human non-small cell lung cancer A549 cell proliferation through PI3K/Akt/mTOR/P70S6K and ERK signaling pathways. *Biochem Biophys Res Commun* 2018;498:616-20.
  27. Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, *et al.* Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): Results from two randomised, double-blind, phase 3 trials. *Lancet Oncol* 2016;17:519-31.
  28. Katakami N, Uchino J, Yokoyama T, Naito T, Kondo M, Yamada K, *et al.* Anamorelin (ONO-7643) for the treatment of patients with non-small cell lung cancer and cachexia: Results from a randomized, double-blind, placebo-controlled, multicenter study of Japanese patients (ONO-7643-04). *Cancer* 2018;124:606-16.
  29. Guney Y, Ozel Turku U, Hicsonmez A, Nalca Andrieu M, Kurtman C. Ghrelin may reduce radiation-induced mucositis and anorexia in head-neck cancer. *Med Hypotheses* 2007;68:538-40.
  30. Zeng Y. Ghrelin may reduce radiation-induced mucositis and anorexia in head-neck cancer: Two sides of a coin. *Med Hypotheses* 2009;72:225-6.
  31. Ozsoy S, Besirli A, Unal D, Abdulrezzak U, Orhan O. The association between depression, weight loss and leptin/ghrelin levels in male patients with head and neck cancer undergoing radiotherapy. *Gen Hosp Psychiatry* 2015;37:31-5.
  32. Lochs H, Dervenis C. Malnutrition – The ignored risk factor. *Dig Dis* 2003;21:196-7.
  33. Arrieta O, Michel Ortega RM, Villanueva-Rodríguez G, Serna-Thomé MG, Flores-Estrada D, Diaz-Romero C, *et al.* Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: A prospective study. *BMC Cancer* 2010;10:50.
  34. Wang X, Han H, Duan Q, Khan U, Hu Y, Yao X. Changes of serum albumin level and systemic inflammatory response in inoperable non-small cell lung cancer patients after chemotherapy. *J Cancer Res Ther* 2014;10:1019-23.
  35. Pastore CA, Orlandi SP, Gonzalez MC. The inflammatory-nutritional index; assessing nutritional status and prognosis in gastrointestinal and lung cancer patients. *Nutr Hosp* 2014;29:629-34.