Effect of Serum Selenium Levels on Radiotherapy-related Toxicity in Patients Undergoing Radiotherapy for Head and Neck Cancer

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Abstract. *Aim: To investigate whether there is a difference in selenium levels before and after radiotherapy (RT) and to study the effects of serum selenium levels on RT-related toxicity in patients undergoing RT for head and neck cancer. Patients and Methods: A population of 47 consecutive patients was enrolled in the study. RT was given by conventional fractionation. RT-related acute toxicity was evaluated once a week. Blood samples were obtained before and after RT to evaluate selenium levels. Results: There was no significant difference between the levels of selenium before and after RT (58.09±1.36 μg/l and 56.34±1.11 μg/l, p-value=0.747, respectively). Grade III-IV mucositis, dysphagia, radiodermatitis, and nausea were seen in 6 (12.7%), 32 (68.2%), 24 (51.1%), and 3 (6.4%) patients, respectively. It was found that there was no statistically significant difference in the levels of selenium before and after RT, and no observed diferrences in regard to RT-related toxicities. Conclusion: The serum selenium levels do not affect RT-related toxicities.*

Radiotherapy (RT), which is an important treatment modality for head and neck cancer, produces antitumour effects by increasing the generation of reactive oxygen species (ROS) (1). Oxidative stress, which results from an increase in ROS, but also a decrease in antioxidants, provokes cell death directly by massive cellular injury to macromolecules, such as lipids, proteins, and nucleic acids, and indirectly by abnormal triggering of cell cycle regulation (2). RT also aims to ensure that tumour cells receive the maximum dose while minimizing radiation exposure to healthy tissues such as skin, gastrointestinal mucosa, and hemopoietic cells, which are relatively radiosensitive and proliferate quickly. RT affects tumour and healthy tissues differently due to the fact that there are important differences in terms of growth and cellular composition between tumour and healthy tissue (3). RT-related toxicity may not be directly associated with patient survival, but reducing acute toxicity does increase a patient's adaptation to the treatment and, importantly, improves the quality of life.

Selenium, an essential trace element, is a very important co-factor in endogenous anti-oxidative systems of the human body (4, 5). It is a structural component of selenocysteine. Selenoproteins, proteins containing one or more selenocysteine residues, play a role in important structural and enzymatic functions (6). Selenium deficiency is associated with increased infection risk and unfavourable emotional conditions, such as depression. In both animal models and humans, it has been shown that selenium has cancer-protective effects and cytoprotective activities. It has been found that selenium has an important role in redox regulation, antioxidant functions, membrane integrity, and protection against DNA injury. Recent studies revealed potential benefits of selenium supplementation in patients with tumours (6).

In this study, we aimed at investigating whether there is a difference the between selenium levels before and after RT and the effects of serum selenium levels on RT-related toxicity, in patients undergoing RT for head and neck cancer.

Patients and Methods

This study was performed at the Department of Radiation Oncology, at the Erciyes University Medical School. A population of 47 consecutive patients undergoing RT for head and neck cancer was enrolled in the study. The study was approved by the Institutional Review Board and was conducted in accordance with the principles

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Table I. *Characteristics of patients with head and neck cancer (n=47).*

Characteristics	
Median age (range), years	58 (33-80)
	n (%)
Gender	
Female	5 (10.6)
Male	42 (89.4)
Cancer location	
Nasopharynx	11 (23.4)
Larynx	23 (49.0)
Hypopharynx	2 (4.3)
Parotid	4 (8.5)
Other salivary gland	1 (2.1)
Lip	1 (2.1)
Oral cavity	1 (2.1)
Maxilla	2 (4.3)
Cancer of unknown primary	2 (4.3)
Stage	
II	5 (10.6)
III	13 (27.7)
IV	29 (61.7)
Pathology	
Squamous cell carcinoma	42 (89.4)
Non-squamous cell carcinoma	5 (10.6)
Radiotherapy	
Curative	28 (60)
Adjuvant	19 (40)
Concomitant chemotherapy	
Presence	32 (68)
Absence	15 (32)

of Good Clinical Practice, as outlined in the Declaration of Helsinki and in accordance to the International Conference on Harmonization guidelines. Informed consent was obtained from each patient.

Radiotherapy and chemotherapy. RT was given through two parallel opposite lateral fields to the cervical lymph nodes, as well as to primary tumour sites and/or through anterior field to the inferior cervical and the supraclavicular lymph nodes. It was given in 1.8-2.0 Gy/day doses, five days a week by conventional fractionation (total 60-70 Gy by spinal cord protection at 46 Gy). Cisplatin at 50 mg/week was concomitantly administered.

Blood samples. Blood samples were obtained before and after RT to evaluate selenium levels. The samples were immediately centrifuged for 10 minutes at 1500 ×*g*. Following the centrifugation, the supernatant was transferred into a new vial. All samples were stored −80˚C until assayed. After thawing, all the samples were diluted ×10 with doubled distilled water (18 MΩ cm) and transferred to Teflon bombs. The analysis of selenium technique was performed by using an inductively-coupled plasma mass spectrometer (Agilent 7500a; Agilent Technologies, Tokyo, Japan). Analyses were performed using an external calibration procedure (7). The assay was able to detect selenium element levels as μg/l. Typical LOD and LOQ were 0.1-0.3 μg/l and 0.3-1.1 μg/l, respectively.

Table II. *Radiotherapy-related toxicities developing during radiotherapy.*

Toxicity	Grade 1 n (%)	2 n (%)	3 n (%)	4 n (%)	Total n (%)
Mucositis	14 (29.8)	17 (36.2)	5 (10.6)	1 (2.1)	37 (78.7)
Dysphagia	5 (10.6)	9 (19.1)	22 (46.8)	10 (21.3)	46 (97.9)
Radiodermatitis	2 (4.3)	20 (42.6)	17 (36.2)	7 (14.9)	46 (97.9)
Nausea	5 (10.6)	6 (12.8)	2 (4.3)	1 (2.1)	14 (29.8)
Weight loss	14 (29.8)	13 (27.7)	0	0	27 (57.5)

Toxicity evaluation. RT-related acute toxicity was evaluated once a week according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. CTC v. 2.0 is available on the NCI/CTEP web site (8).

Statistical analyses. The SPSS 15.0 software (SPSSFW; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Continuous variables with normal distribution are presented as the mean±SD. The median value is provided when a normal distribution is lacking. Qualitative variables are given as percentages. Because the distribution of RT-related toxicities was not homogenous, the toxicities were divided into groups, namely the presence and absence of mucositis, nausea, and weigh loss; and grade I-II and grade III-IV for dysphagia and radiodermatitis. Statistical analysis for association between the levels of selenium before and after RT was performed by the paired *t*-test. Similarly, the associations between the levels of selenium and RT-related toxicities were evaluated by the Student's *t*-test. A *p*-value of 0.05 was considered statistically significant.

Results

The characteristics of the patients are given in Table I. The median patient age was 58 (range=33-80) years. Most of the patients were males. Laryngeal and nasopharyngeal carcinoma were the most common types of tumour. For most of the patients, the histopathological diagnosis and stage of cancer were squamous cell carcinoma and stage IV, respectively. Twenty-eight (60%) out of the 47 patients underwent curative RT. Concomitant chemotherapy was given to 32 (68%) patients.

Table II shows RT-related toxicities developing during RT. Grade III-IV mucositis, dysphagia, radiodermatitis, and nausea were seen in 6 (12.7%), 32 (68.2%), 24 (51.1%), and 3 (6.4%) patients, respectively. No grade III-IV weight loss was observed, while grade I-II weight loss was seen in 27 (57.5%) patients.

There was no significant difference between the levels of selenium before and after RT (58.09±1.36 μg/l and 56.34±1.11 μg/l, *p*-value=0.747, respectively).

It was found that there was no statistically significant association between the levels of selenium before and after RT and RT-related toxicities (see Table III).

Discussion

Combined-modality chemoradiotherapy of squamous cell carcinomas of the head and neck is complicated due to toxicity to normal tissue (8). Despite the availability of sophisticated intensity-modulated radiotherapy treatment techniques and frameless stereotactic radiotherapy modalities, such toxicity remains a dose-limiting problem in therapeutic programs (9). The adverse effects of RT and chemotherapy in patients with cancer are associated with the generation of free oxygen radicals and oxidative injury to normal cells (10).

Selenium is a co-factor of the enzyme glutathione peroxidase (GSH-Px), which is important for the detoxification of free radicals. GSH-Px, a tetrameric enzyme containing four selenium atoms, is localized in the cytosol. It has been shown that a decrease in GSH-Px is associated with an increase in RT-related toxicity (5).

Selenium exerts radioprotective effects in normal tissues as well as anti-oedematous and prognostic effects. In addition, it increases the radiosensitivity of malignant tumours and has primary and secondary anticancer effects (6). It is debatable whether selenium has a protective role against both acute and chronic adverse effects of RT. Selenium compounds have been evaluated as biological response modifiers and toxicity antagonists for the prevention of chemotherapy- and RT-related adverse effects (11). *In vitro* studies showed that sodium selenite has a cytoprotective effect on human fibroblasts and endothelial cells, without any decrease in the efficacy of RT against cancer cells (12, 13). Sagowski *et al*. showed that parenteral sodium selenite reduces acute radiogenic damage of rat parotid glands during fractionated irradiation, with better gland function post-irradiation (14).

The reference range of serum selenium levels is reported to be 65-135 μg/l (5). In Turkey, there are no data regarding normal serum selenium levels in healthy persons. Several studies have revealed that serum selenium levels were lower in patients with head and neck cancer than those of healthy persons (15-21). In this study, the mean serum selenium levels were 58.09±1.36 μg/l in patients with head and neck cancer, and this value is lower than the reference range.

It has been observed that although there may be selenium deficiency due to cancer before treatment in most patients with cancer, this is not exacerbated by standard RT (5, 20).

In another study in which the effect of RT on serum selenium levels was investigated in 40 patients with head and neck cancer, it was reported that the serum selenium levels before and after RT were 61.99±1.57 μg/L and 62.29±1.61 μg/l and there was no difference between the two periods (5). In our study, the non-significant decrease in serum selenium levels after RT is similar to that of studies reporting that RT does not further reduce serum selenium levels.

Table III. *Associations between the level of selenium before and after radiotherapy and radiotherapy-related toxicities.*

Toxicity	*p*-Value	
	Before RT	After RT
Mucositis	0.177	0.890
Dysphagia	0.162	0.706
Radiodermatitis	0.370	0.850
Nausea	0.198	0.263
Weight loss	0.727	0.563

RT: Radiotherapy.

There are a few studies on the clinical effects of selenium regarding toxicities resulting from the generation of free oxygen, induced by chemotherapy and RT. In one study in which the effects of selenium substitution in the prevention of RT-associated toxicities were evaluated in 39 patients with head and neck cancer, it was observed that selenium had limited effects in the prevention of loss of taste and dysphagia (21). In a prospective randomized study performed by Micke *et al*., it was noted that sodium selenite supplementation was beneficial in RT-induced diarrhea and selenium deficiency in patients undergoing adjuvant pelvic RT for cervical and uterine cancer (4). In this study, we did not observe any significant effects of serum selenium on RT-related toxicities.

There is not enough evidence that selenium supplementation reduces the adverse effects of tumour-specific chemotherapy or RT. Therefore, it is not possible to make a recommendation on selenium supplementation for patients with cancer. In addition, the potential risks of an essential trace mineral supplementation need to be considered (4). Similarly, our study, which found no significant association between the serum selenium levels and RT/chemotherapy-related toxicities does not establish a basis for selenium supplementation.

In conclusion, the serum selenium levels are not influenced by RT and serum selenium levels do not appear to affect RT-related toxicities, therefore it is supposed that selenium supplementation may not be effective in the prevention of RT-related toxicities.

Conflicts of Interest

No potential conflicts of interest were disclosed.

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