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The Effect of Selenium Serum Levels on Oral Mucositis Frequency and Severity in Patients with Head and Neck Radiation

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ABSTRACT

Background: Radiotherapy as an important treatment modality in head and neck cancer diminishes reactive oxygen system which causes damages to the normal cell/tissue function and cell cycle regulation. Selenium involve in both antioxidant and anti-inflammatory systems. In this study, we aimed to investigate whether there is a difference between selenium levels before and after radiotherapy and the effects of serum selenium levels on radiotherapy oral mucositis (OM) patients undergoing radiation for head and neck cancer.

Methods: This prospective study includes 42 head and neck cancer patients treated by external beam radiotherapy at the Cancer Institution of Imam Khomeini Hospital, Tehran University of Medical Sciences. Plasma selenium concentrations were determined before and after radiotherapy. The grade of oral mucositis was evaluated weekly from the first day until resolving OM by the WHO oral toxicity scale.

Results: The mean patient age was 54.7±13.2 years. For most of the patients, the histopathological diagnosis of cancer was squamous cell carcinoma (N=28 (66.7%)). There was no significant difference in serum Selenium levels before and after radiotherapy (85.4±30.6 before radiation and 90.3±33.3 after radiation, P >0.05). Moreover, there was no significant difference between levels of Se after radiotherapy in patients who developed severe oral mucositis and who did not.

Conclusion: In our study, we couldn't find any significant difference in the levels of Selenium before and after radiotherapy and also there was no association between Selenium levels and oral mucositis developing.

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Introduction

Head and neck cancer is the third most common cancer in the world which has an increasing trend in Iran (1, 2). Radiotherapy (RT) is one of the most important modality in head and neck cancer treatment and it works as a cell killer through the generation of reactive oxygen system (ROS). Free radicals produced by RT provoke damage to the normal cell/tissue function and cell cycle regulation (3, 4).

RT-related toxicity may reduce patients 'compliance to treatment and the quality of life. In addition, it leads to unplanned interruption of treatment. Oral mucositis (OM), explained as a painful inflammation and ulceration of the

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mucous membranes, with an incidence of 80-97% is the common and critical side effect of head and neck radiation (5).

OM begins in the submucosa and progress to the epithelium. This biological event can be divided into sequential five phases: initiation, message generation, signaling and amplification, ulceration and finally healing. Injuries to the mucosal cells appear to be a result of the generation of oxidative stress and reactive oxygen species (6). However, production of pro-inflammatory cytokines including TNF-α, and the ILs (IL-1, IL2, and IL-6) have some roles in the development of OM (7).

Selenium (Se), an essential trace element, involve in both antioxidant and anti-inflammatory systems. Se exerts radio protective effects in normal tissues and it is well known to be an integral component of the enzyme glutathione peroxidase, which plays an important role in cellular defense against oxidative damage (8-10). Many studies showed a cytoprotective effect of selenium and its important role in redox regulation, antioxidant functions, membrane integrity, and protection against DNA injury (11). Some studies have reported that RT had effects on the antioxidant/oxidant system including Se and it alters the Se level (12-15).

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

Methods

This study was performed at the cancer institution of Imam Khomeini Hospital, Tehran University of Medical Sciences from January to December 2017. A population of 41 consecutive patients undergoing RT for head and neck cancer was enrolled in the study. Patients aged 18-85 years old who received at least two-thirds of the oral cavity radiation enrolled in this study. Before enrollment, the participants and their guardians were fully informed of the research purpose and written consent was obtained. They were assured that their personal information would be confidential.

The radiation protocol in all participants was conventional RT techniques, 5 fractions per week at 60Gy and below and more than 60Gy cumulative doses over 6 to 7 weeks with or without cisplatin (30-50mg/m^2 weekly, during radiation) as a radio-sensitizer. Demographic data including age and sex, type of cancer, and radiation cumulative and dose per fraction were collected at first visit.

Serum samples were obtained from patients at baseline and within 24 hours of the end of radiotherapy. The serum samples were stored in two separate micro tubes at -80°C until selenium assay was done. The serum selenium level was determined by the graphite furnace atomic absorption spectrometry (Agilent atomic absorption, Germany, Selenium level reported in mcg/L). The serum selenium levels below 65µg/l were considered to be deficient (16).

The grade of OM was evaluated weekly by the WHO oral toxicity scale (17). The WHO scoring was done as follows: grade zero= normal, no OM; grade 1= soreness and erythema; grade 2= erythema, ulcers, can eat solids; grade 3= ulcers, requires liquid diet only; grade 4=alimentation not possible) (18).

The oral status and objective or subjective symptoms of each patient were evaluated on the first day and then on a weekly basis until radiotherapy finished, and then after one month to determine the incidence, severity, and duration of OM in the participants.

The SPSS software was used to analyze the data. The one-way analysis of variance (ANOVA) was calculated the impact of different total RT doses and other factors on Se level and Cox regression were done to find associations between different parameters and developing severe OM. P-values less than 0.05 were considered significant.

Results

The results of 41 patients were evaluated in this study. One of the patients discontinued radiotherapy due to personal preference. The mean patient age was 54.7±13.2 (range=18-81) years. For most of the patients, the histopathological diagnosis of cancer was squamous cell carcinoma (N=28 (66.7%)). Participants' characteristics are displayed in Table 1. Seventeen (41.4%) out of the 41 patients underwent concurrent chemotherapy. Among patients who were received concurrent chemotherapy one patient stop and three delayed their RT due to OM.

Almost all patients experienced some degrees of OM. Table 2 shows OM developing during RT. Grade III-IV mucositis (severe OM), was seen in 19 (46.34%) patients.

There was no significant difference in serum Selenium levels before and after RT (85.4±30.6 mcg/l before radiation and 90.3±33.3 mcg/l after radiation (P: 0.51). Moreover, there was no significant difference between levels of Se after RT in patients who developed severe OM and who did not. (Selenium levels in patients with severe OM: 96.6±29 mcg/l, patients without severe OM: 88. 8±37.3 mcg/l, P: 0.24).

Fourteen (33%) patients had Selenium levels below 65mcg/l before RT and 5 (14%) patients were experienced Selenium deficiency after RT. There was no difference in time of developing severe OM between who had Selenium deficiency (before and after RT) and others (P<0.05).

However, in Cox regression analysis association, there was no significant correlation between severe OM developing and age, gender, total radiation dose, radiation dose per fraction and also Selenium level before RT (P>0.05).

The impact of different total RT doses and other factors on Se level were analyzed. The comparison indicated that there were not any significant differences between subgroups. The mean Selenium levels in different subgroups were shown in Table 3.

Table 1. Baseline characteristics of the patients.

Characteristics	Patients (N= 41)
Sex, N (%)	
Male	28(66.7)
Age, year	
Mean ±SD	54.7±13.2
Median	57.5
Minimum-Maximum	18-81
Cancer type, N (%)	
SCC	28 (66.7)
NPC	5 (11.9)
ADC	4 (9.5)
Sarcoma	1 (2.4)
Neuroblastoma	1 (2.4)
Metastasis of other cancers	2 (4.8)
Total radiation dose, N (%)	
≤6000 Gy	20 (47.6)
>6000 Gy	21(50.0)
Dose per fraction	
1-2 Gy	28 (66.7)
3 Gy	13 (31.0)
Concurrent Chemotherapy, N (%)	17 (41.4)
Selenium level before radiation	
Deficient (<60 mcg/l)	14 (33.3%)
Sufficient (≥60 mcg/l)	27 (64.3)
Selenium level after radiation	
Deficient (<60 mcg/l)	6 (14.3)
Sufficient (≥60 mcg/l)	27 (64.3)
Missing data	8 (19.5)

ADC: Adenocarcinoma, NPC: nasopharyngeal carcinoma, SCC: Squamous cell carcinomas,

Table2. Oral mucositis (OM) characteristics (Mean ± SD).

Duration of OM, Grade 1-4 (day)	50.44±17.56
Duration of severe OM, Grade 3,4 (day)	14.00±13.67
Onset of OM (week)	1.70±1.05
Recovery (day after radiation completion)	8.88±11.09

Discussion

In this prospective study, 41 patients with head and neck cancer who received RT were evaluated. OM developed in almost all patients and the Selenium level did not have an impact on severity and incidence of OM. Evaluation of serum Selenium level could not show any difference before and after RT.

An essential trace element, Selenium, is a very vital cofactor in endogenous anti-oxidative systems of the human body (19). It is a structural component of selenocysteine. Selenoproteins, proteins comprising one or more selenocysteine residues, have a part in main structural and enzymatic roles (20). In human and animal models, it has been shown that selenium has cytoprotective functions. It has been found that Selenium has an imperative role in redox regulation, antioxidant functions, membrane integrity, and defense against DNA injury (19, 20).

Franca et al., showed that the significant reduction in plasma levels of Selenium is recorded in patients with breast cancer undergoing radiotherapy (21). Yadav et al., show that all subjects (30 people) in their study had serum Selenium levels significantly lower as compared with controls, and these levels decreased further as tumor burden increased. Levels came within normal range after one year of radiotherapy in 10 patients who were cured but in the remaining patients who had residual disease, levels remained persistently low (22).

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 61.9±1.6 mcg/l and 62.3±1.6 mcg/l and there was no difference between the two periods (16). Celalettin et al., reported no significant difference between the levels of Selenium before and after RT and no observed differences in regard to RT-related toxicities (23). In our study, the non-significant difference in serum Selenium levels before and after RT is similar to studies reporting that RT does not further reduce serum Selenium levels.

Table 3. Radiotherapy impact on serum Selenium levels in different subgroups.

Characteristics	Sub index	Mean ± SD(mcg/l)	P value
Sex	Male	96.2±27.8	0.43
	Female	100.6±31.8	
Total radiation dose	≤6000 Gy	96.9±38.2	0.59
	>6000 Gy	90.6±28.4	
Dose per fraction	1-2 gy	85.6±33.2	0.54
	3 gy	92.8±27.4	
Concurrent chemotherapy	No	100.8±35.4	0.33
	Yes	85.3±27.9	

Studies showed cumulative doses of radiation have a crucial effect on the severity and onset of OM. At cumulative doses of 10 Gy, erythema appears and patients feel a burning sensation. After about 2 weeks when the patient has received 30 Gy of radiation, unbearable complications appear (24, 25). In this manner, in our study, mean onset of OM was between the first and second weeks of RT.

According to cell culture analyses, selenium acts as a normal cell radio-protectant and high concentrations of sodium selenite in endothelial cells decrease the effects of radiation and highlight the possible normal cell protective effect of Selenium in radiation (26, 27). According to this survey, there was no significant difference in the plasma concentration of Selenium between patients who suffer from severe OM and others and sufficient levels of Selenium could not postpone severe OM. Therefore, the ineffectiveness of Selenium in reducing radiation OM might be due to the insufficient Selenium concentration in target cells and plasma concentration is not a good indicator for predicting adverse effects of RT.

Studies reported three plasma biomarkers for assessing Selenium nutritional status, selenoprotein P, glutathione peroxidase-3, and plasma selenium which respond differently to Selenium intake and yield different information (28-30). Burk et al., showed that Selenium plasma level did not correlate with selenoprotein and selenium nutritional status. However, the consumption of plant foods rich in selenomethionine influences plasma Selenium (30). In this study, although we just evaluated Selenium plasma level, RT may have effects on others parameter of Selenium status in the human body. RT could not decrease the Selenium level in our patients. The Selenium food content and nutritional habit varied among our patients so, it may lead us to invalid conclusions about Selenium alteration during RT.

In conclusion, the serum Selenium levels are not influenced by RT and serum Selenium levels do not appear to affect RT-related toxicities. Further Studies with more participants and controlling confounding factors like patient nutritional habits and chemotherapy are needed to show the correlation between RT and Selenium status, precisely. Assessing other Selenium plasma biomarkers may clarify the correlation between RT related OM and Selenium status.

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