

Consequences of radiotherapy on nutritional status, dietary intake, serum zinc and copper levels in patients with gastrointestinal tract and head and neck cancer

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ABSTRACT

Objectives: Malnutrition occurs frequently in cancer patients and is multifactorial and can lead to negative outcomes. So we studied the effect of radiotherapy on nutritional status, weight changes, dietary intake, serum zinc and copper levels.

Methods: During the period of October to March 2005, 45 cancer patients who referred to the Radiotherapy Center, Imam Khomeini Hospital, Iran were recruited. We assessed the nutritional status of patients using Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire. Patients on the basis of location of radiotherapy classified to mediastinum, head and neck and pelvic groups. Changes in dietary intake (using 24-hour recall method) and body weight were evaluated prior to and during radiotherapy. At the onset and the end of radiotherapy, serum levels of zinc, copper and albumin were determined.

Results: After treatment malnutrition increased significantly in all patients ($p=0.01$) and in head and neck ($p=0.007$) and pelvic groups ($p=0.04$). The decreased body weight of patients was significant in the head and neck ($p=0.02$), and pelvic groups ($p=0.005$). The mean daily energy and protein intake of head and neck and pelvic groups decreased during radiotherapy while energy intake increased significantly in mediastinum group ($p=0.01$). After treatment, significant decreases also observed in mean serum zinc, copper and albumin levels ($p<0.05$).

Conclusion: Because of the negative effect of radiotherapy on oral feeding, nutritional assessment and intervention should be an integral part of treatment. Also, it would be worthwhile studying the effect of zinc supplementation on dietary intake and nutritional status of patients.

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During the past few decades, important advances have been made in effort to improve early detection of cancer and increase the efficiency of antineoplastic regimens.¹ Consequently, supportive care is becoming increasingly important in the management of patients with cancer, and oncologist now aim to positively influence quality of life and nutritional status as well as survival.² It is widely recognized that diet and nutrition play significant roles throughout the clinical course of cancer.³ The incidence of malnutrition in patients with cancer ranges from 31 to 87%.⁴ The risk of malnutrition and its severity are affected by tumor type, stage of disease and the antineoplastic therapy applied.⁵ Moreover, cancer-associated malnutrition has many consequences, including increased risk of complications, decreased response and tolerance to treatment, a lower quality of life, reduced survival and higher health care costs.⁵⁻⁷ Radiotherapy can be an important component of cancer treatment for cure, prolongation of life or pain control;⁸ however, it has clinical limitations due to its adverse effects, mainly damage to normal tissues.⁹ Gastrointestinal tract, head and neck cancer patients being treated with radiotherapy are at an increased risk of malnutrition due to the severe side effects.¹⁰ There are few publications on the nutrient intake and nutritional status during curative radiotherapy among cancer patients. These observations therefore encourage the careful evaluation of all cancer patients who are candidates for radiotherapy. Many researchers have demonstrated the critical role of zinc, in diverse physiologic processes, such as growth and development, maintenance and priming of the immune system, and tissue repair.¹¹⁻¹³ Zinc is a ubiquitous trace metal required for the activity of over 300 metalloenzyme,¹³ the structural constituent of many proteins, and in

preventing free radical formation.¹⁴ Therefore, zinc is a pivotal element in ensuring the functioning of various tissues and organs, including the immune response.¹² Consequently, deficiency of zinc may result in increased wound complications, reduced appetite and food intake, impaired taste and smell, cell-mediated dysfunction in humans¹⁵ and increased rates of tumor development in experimental animals.¹⁶ Considering the importance of malnutrition in decreased response and tolerance to anticancer treatments, and taking into account the essential roles of zinc in immune system, taste and appetite loss and significant interactions between zinc and copper,¹⁷ the present study was conducted to determine nutritional status in cancer patients during radiotherapy and compare serum zinc and copper levels before and after radiotherapy.

Methods. This prospective study was approved by the Ethics Committee of Tabriz University of Medical Sciences. During the period of October to March 2005, 45 (32 males and 13 females) volunteers cancer patients with mean age of 54.4 ± 17.6 years who referred to the radiotherapy center of Imam Khomeini hospital were recruited. Before radiotherapy planning, radiation-oncologist registered patients' clinical variables, cancer location and tumor size, nodes, metastasis (TNM) staging. Patients on the basis of location of radiotherapy classified to: mediastinum, head and neck and pelvic groups. Therapy was performed as 1.8 or 200 gray (Gy) per day, 5 days a week, for 6 weeks. Patients' diagnoses, tumor staging and radiotherapy protocol are shown in **Table 1**. A prior to and during radiotherapy, single nutritionist assessed nutritional status as described below: height was measured using a mounted tape with the subject arm hanging freely at their sides and recorded to the nearest 0.5 cm. Body weight of subjects were measured bare foot and light clothing to the nearest 0.1 Kg with a Seca scale. Weight measurements in patients were before and up to 6 weeks of therapy. Nutritional

status was assessed by Ottery's Patient-Generated Subjective Global Assessment (PG-SGA) which is a validated nutritional assessment tool for cancer patients⁶ which addresses: 1) weight changes, symptoms (anorexia, nausea, constipation, mouth sores, vomiting, diarrhea, dry mouth, hypogeusia and dysphagia), alterations in food intake and functional capacity 2) Components of metabolic stress (sepsis, neutropenic or tumor fever, corticosteroids), and physical examination, subcutaneous fat, ankle/acral edema, or ascites. This tool categorizes the nutritional status as normal, moderate or severe malnutrition. Then patients were interviewed and the questionnaire completed at the onset and the end of radiotherapy. Dietary intake was assessed using a 24-hour recall food questionnaire for 3 days of week which was taken from patients prior to and during radiotherapy, and were analyzed for energy, protein intake by using Nutrition III for Windows Soft-ware. Blood samples for biochemical parameters were collected after an overnight fast (12 hours) into tubes before radiotherapy and at the end of therapy. The samples were centrifuged at 2000 g for 15 min, and off-the-clot serum samples without hemolysis were removed with a micropipette. The serum samples were kept at -32°C until biochemical determinations. Serum zinc and copper were determined by an atomic absorption spectrophotometer against standard references.¹⁸ Serum albumin was measured by Colorimetric method.¹⁹ Before completing the questionnaire, the reliability analysis was performed to determine the extent to which items in the questionnaire were related to each other. The scale reliability was estimated with Cronbach's alpha coefficient. The Cronbach reliability coefficient was 0.754, which showed that the items were highly correlated. Descriptive statistics were obtained for all study variables for each study group. The comparison of body weight, energy and protein intake during the treatment was analyzed by repeated measures Analysis of Variance. Wilcoxon Signed Ranks Test and Paired-

Table 1 - Patients' diagnoses, tumor staging and radiotherapy treatment protocol (n=45).

Location	n	(%)	Staging (n)	Dose (CGy)	Day	Site of treatment
Esophagus	11	(24.4)	I (1) III (7) IV (3)	6500	35	Mediastinum
Head and neck	22	(48.9)	I (1) II (4) III (4) IV (5) stage X (8)	7000	35	Head and neck
Colorectal	12	(26.7)	II (5) III (5) IV (2)	6500	35	Pelvic

Table 2 - Nutritional status of patients at onset and the end of radiotherapy.

Nutritional status	Mediastinum (n=11) %		Head and neck (n=22) %		Pelvic (n=12) %		Total (n=45) (%)	
	Onset	End	Onset	End*	Onset	End†	Onset	End‡
Well nourished	18.2	27.3	40.9	22.7	50	33.3	37.7	26.7
Moderate malnutrition	36.4	27.3	40.9	27.3	25	16.7	35.6	24.4
Sever malnutrition	45.4	45.4	18.2	50.0	25	50.0	26.7	48.9

Wilcoxon signed ranks test, *p=0.007, †p=0.04, ‡p=0.01‡ in comparison with pre-radiotherapy.

Table 3 - The zinc, Copper and albumin levels in cancer patients before and after radiotherapy.*

Location of radiotherapy	Zinc (µg/dl)		P value†	Copper (µmol/l)		P value†	Albumin (gr/dl)		P value†
	Before	After		Before	After		Before	After	
Mediastinum (n=11)	112.5±4.2	91.1±6.09	0.02	28.9±2.8	22.6±1.7	0.11	3.5±0.1	2.9±0.1	0.006
Head and neck (n=22)	110. ±8.4	90.4±4.9	0.03	23.9±1.4	22.9±1.3	0.2	3.7±0.1	3.2±0.07	0.001
Colorectal (n=12)	95.9±13	78±4.7	0.21	23.6±1.9	20.8±1.7	0.15	3.9±0.1	3.4±0.1	0.009
Total (n=45)	106.3±5.9	87.0±3.1	0.002	26.4±1.4	22.3±0.9	0.003	3.8±0.07	3.2±0.05	0.001

*values are expressed as mean±SEM, †Comparisons with pre-radiotherapy using paired-t-test.

t-test were used to compare nutritional status and biochemical factors respectively at the onset and the end of radiotherapy. A probability-value of less than 0.05 was considered statistically significant.

Results. Patients' nutritional status categories at the onset and the end of radiotherapy according to the location of radiotherapy are presented in **Table 2**. In general, after radiotherapy, incidence of malnutrition (moderate and sever malnutrition) in patients increased significantly (62.3 to 73.3%, $p=0.01$). Before treatment, malnutrition was observed in 81.8%, 59.1% and 50% of patients in mediastinum, head and neck and pelvic group, respectively, which changed to 72.7%, 77.3% and 66.7% of patients at the end of radiotherapy. The percentage of increases in malnutrition were statically significant ($p=0.007$ and $p=0.04$). The changes in patient's body weight during radiotherapy on the basis of location of radiotherapy are shown in **Figure 1**. Mean body weight of patients in head and neck and pelvic groups significantly decreased during radiotherapy ($p=0.02$ and $p=0.005$). However, weight loss was not significant in the mediastinum group. The mean energy and protein intake of patients prior to and during radiotherapy are presented in **Figure 2** and **Figure 3**. The mean daily energy and protein intake of

the mediastinum group declined during the first week and then increased from the second week to the end of therapy, which changes in energy intake during the treatment was significant ($p=0.01$). The mean daily energy and protein intake of the head and neck group decreased significantly during the radiotherapy ($p=0.005$ and $p=0.01$). The mean daily energy and protein intake in the pelvic group decreased insignificantly during the treatment. The serum zinc, copper and albumin levels in cancer patients before and after radiotherapy are expressed in **Table 3**. Overall, the mean serum zinc in cancer patients was significantly lower than before the treatment ($p=0.002$). After the radiotherapy, the mean serum Zn in mediastinum and head and neck groups decreased significantly ($p=0.02$, $p=0.03$). The remarkable but statistically insignificant decreased in serum Zn was also observed in the pelvic group. In general, the mean serum copper levels in patients decreased significantly after radiotherapy ($p=0.003$). The mean serum Cu decreased insignificantly in all groups after radiotherapy. After the treatment, the mean serum albumin in all groups decreased significantly ($p<0.05$) as compared with levels of pre-radiotherapy.

Discussion. The cancer patients may be at high malnutrition risk during the course of disease and

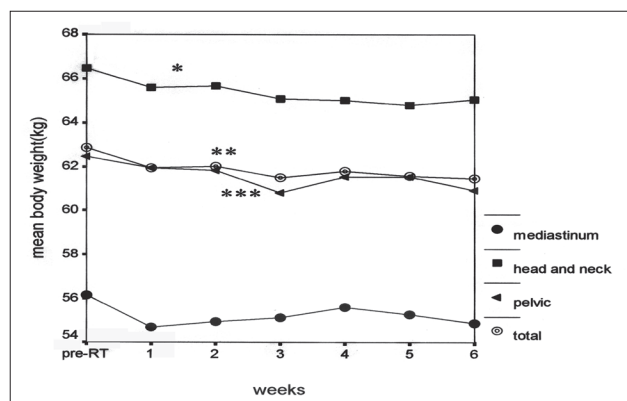


Figure 1 - Changes in the body weight of subjects during therapy. Changes from the start to the end of radiotherapy, repeated measures Analysis of variance, * $p=0.02$, ** $p=0.001$, *** $p=0.005$.

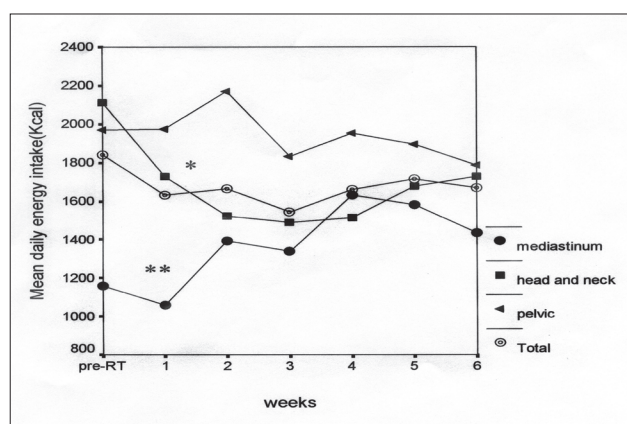


Figure 2 - Changes in mean daily energy intake during therapy. Changes from the start to the end of radiotherapy, repeated measures Analysis of variance, * $p=0.005$, ** $p=0.01$.

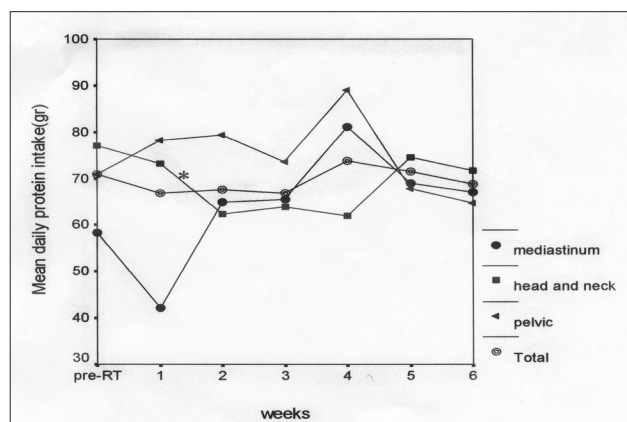


Figure 3 - Changes in mean daily protein intake during therapy. Changes from start to end of radiotherapy, repeated measures Analysis of variance, * $p=0.01$.

especially during radiotherapy.⁵ The profound negative influence of malnutrition on cancer treatment is well recognized, with nutritional deficiencies impacting on all modalities of treatment.⁷ This study identified malnutrition in 62.3% of patients (35.6% moderate and 26.7% severe malnutrition) by using the PG-SGA at the beginning of treatment. Our finding is consistent with that Segura et al²⁰ who noted a 52% and with that of Bauer et al²¹ noted a 79% prevalence of malnutrition in cancer patients. Before therapy, we observed malnutrition in 81.8%, 59.1% and 50% of patients in mediastinum, head and neck and pelvic groups, respectively. These results are in agreement with data published by other researchers.^{4,22-24} After radiotherapy, incidence of malnutrition significantly increased in patients receiving radiation therapy to the head and neck and pelvic. These results support the observations of previous studies.^{25,26} Our results indicated the improvement in the nutritional status of patients with esophageal cancer treated with radiotherapy which may be due to tumor response to radiotherapy and improvement in dietary intake. In our study, patients in head and neck and pelvic groups, experienced significant weight loss during radiotherapy ($p<0.05$). Our findings are in agreement with the previous studies.^{9,27,28} Pie et al⁹ reported that patients receiving pelvic radiotherapy had an average weight loss of 1.4 Kg during treatment. Guren et al²⁷ observed a significant weight loss (<1 Kg) in patients with rectal cancer during radiotherapy treatment. Shi et al²⁸ noted a significant decrease in the mean body weight (3.1 kg) of the patients with head and neck cancer during radiotherapy. Also a significant weight loss in patients during radiotherapy has been reported by other researchers.^{4,29,30} In the present study, the mean daily energy and protein intake of head and neck group decreased significantly during radiotherapy ($p=0.005$, $p=0.01$). The result of our study supported the observations of previous investigators who had already reported a significant decrease in caloric intake of patients during radiotherapy.³⁰⁻³² Eating problems in patients with head and neck cancer increased towards the end of radiation treatment period³³ and it is likely that the reduced energy and protein intake were most pronounced at the end of the treatment period. In our study, the mean daily energy and protein intake in the pelvic group decreased insignificantly during treatment. Our findings are consistent with that of Pie et al,⁹ who reported caloric intake diminished in patients receiving radiation therapy to the pelvic but the changes in caloric ingestion were not significant, Guren et al²⁷ and Ravasco et al²⁶ also reported energy intake of patients with colorectal cancer decreased significantly during radiotherapy. We thought that insignificant decrease of energy intake in pelvic group in our study and Pie et

al⁹ may be due to small sample size. There are few publications on the dietary intake during curative mediastinum radiotherapy. Our findings showed that the mean daily energy and protein intake of mediastinum group declined during the first week and then increased from the second week to the end of therapy which changes of energy intake during treatment were significant. Possible explanation to our findings might be that, before therapy, 90% of patients with tumors of esophagus already had a markedly reduced dietary intake³⁴ whereas the improvement in the dietary intake of patients in mediastinum group which may be due to positive effect of radiotherapy on tumor size. After radiotherapy, the mean serum Zn levels of patients were significantly lower than before treatment. The mean serum zinc in mediastinum and head and neck groups decreased significantly after treatment. The remarkable but statically insignificant decreased in serum Zn in pelvic group was also observed. These results are in agreement with data published by other investigators.^{35,36} Hsu et al³⁵ evaluated the levels of serum zinc in patients with nasopharynx carcinoma before and after radiotherapy and through out radiotherapy. They found that the levels measured after radiotherapy became significantly lower than those before radiotherapy. Ertkein et al³⁶ reported plasma Zn levels in patients with head and neck cancer decreased significantly the day after the beginning of radiotherapy.

A few hypotheses could be offered to explain the decreased levels of serum Zn: we could speculate that the decreased circulating Zn might be used up in the attempt to counteract the enhanced free radical production in the radiation affected tissues. The other speculations are that the decreased serum Zn may be due to low serum albumin, response to stress and inadequate Zn intake.³⁷ Overall, after radiotherapy the mean serum Cu decreased significantly as compared with level of pre-radiotherapy. These results are in agreement with data published by other researchers.^{35,38} In the present study, the mean serum Cu also decreased insignificantly in all groups after radiotherapy. These findings supported the observations of previous studies of Shu et al³⁰ and Horst et al³⁹ who reported insignificant decreases in serum Cu levels of patients treated with radiotherapy. The results of the present study showed that the levels of albumin were significantly lower in serum of all groups as compared to the pre-radiotherapy. The results of several studies indicated that the albumin levels in the blood of different type of cancer were significantly reduced as compared with pre-radiotherapy.^{27,40} Low albumin levels have been associated with increased mortality for patients with certain types of cancer.⁴¹ The possible causes of hypoalbuminemia in patients have been attributed to insufficient protein intakes,⁴² increased vascular

permeability due to cytokine-induced endothelial cell injury, or to discrete acute phase response resulting decreased in albumin synthesis by the liver in favor of acute-phase protein.⁴³ Additionally, albumin is a major source of sulfhydryl groups and these thiol scavenge free oxygen,⁴⁴ which was produced by radiotherapy. According to our results the nutritional assessment of cancer patients during radiotherapy is indispensable because they have a high prevalence of malnutrition and a suitable and adapted nutritional support may be needed. Also, it would be worthwhile studying the effect of oral zinc supplementation on dietary intake and nutritional status of patients.

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