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RESEARCH ARTICLE

KNOWLEDGE AND BELIEF ON ANTIOXIDANT PRESCRIPTION BY MEDICAL AND RADIATION ONCOLOGISTS IN CANCER PATIENTS

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ABSTRACT

Background: Radiotherapy and Chemotherapy have been first-line therapy for many decades in the treatment of stage III head and neck cancer. Management of complications associated with these therapies and the disease itself is a major challenge for healthcare professionals. Literature survey revealed that there is controversy related to administration of antioxidants in chemoradiotherapy.
Aims and Objectives: The present study was planned with the objective of knowing knowledge & beliefs of the medical and radiation oncologists towards prescribing antioxidants in head and neck cancer patients.
Materials and Methods: A survey was conducted among 30 medical and radiation oncologists working in Oncology hospitals in Hyderabad utilizing an organized questionnaire embroiling the present utilization of antioxidants and palliative care in cancer therapy. The questions when answered were later retrieved and statistically analyzed.
Statistical Analysis: Mann Whitney U test (Z test).
Results: 75% of medical oncologists and 67% of radiation oncologists preferred naturally available form of antioxidants during cancer therapy. 60% of Radiation oncologists recommended antioxidants after radiotherapy. 83% of medical oncologists believe that antioxidants can reduce immunological complications associated with cancer chemotherapy while 66% of radiation oncologist opined that they can reduce mucositis.
Conclusion: The present study highlighted that the naturally available antioxidants were preferred by medical & radiation oncologists, as the nutrition rich in antioxidants is trivial in cell protection and repair and would support the natural body's defense mechanism. As the controversy over the concurrent use of antioxidants with chemotherapy or radiotherapy still exists, a demand for randomised controlled studies prevails.

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INTRODUCTION

Oncologists are enquired commonly regarding the side effects of cancer chemo-radiotherapy by the patients and urge them to reduce the burden of side effects of treatment. (D'Andrea, 2005) Dietary antioxidants form a minor portion in the diet of patients with or without prescription. (D'Andrea, 2005) Many oncologists opinioned that antioxidants by their nature undermine the free radical mechanism of radiotherapy and should therefore generally be avoided during treatment, some believe that antioxidants taken during cancer treatment might alleviate some of the adverse effects of the treatment but could even hinder the efficacy of cancer therapy. (Moss, 2007) The supplementation of antioxidants during radiation therapy poses a confusing and difficult problem for the radiation oncologists, as these antioxidants which are known to protect the normal cells from reactive oxygen species might also provide the same benefits to the cancer cells and hence reduce the efficacy of treatment. New discoveries propose that antioxidants initiate apoptosis in growth cells and shield patients from agonizing symptoms of radiation treatment. (Borek, 2004) The controversy in relation to usage of these supplements during cancer treatment is still persistant though recent evidence of such prescriptions on patient was direct and compelling. (Lawenda *et al*., 2008) Hence, a questionnaire study was designed to analyze the current status of advocating

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antioxidants in prescriptions during cancer palliative care by medical and radiation oncologists in Hyderabad.

MATERIALS AND METHODS

Design: A survey was conducted among medical & radiation oncologists of Hyderabad using a structured questionnaire. A total of 10 questions were administered in the study to 30 oncologists whose identity was ensured confidentially.

Participants: Out of those 30 oncologist participants, Medical oncologists were 6 and Radiation oncologists were 24. A questionnaire was designed after an informal discussion with the peers and experts in the field of Oral Medicine and Radiology. This questionnaire was reviewed and suitable modifications were made in the design of the questionnaire. It was initially used on a small group of oncologists to eliminate bias and with specific recommended modifications and determining the reliability and validity of the questionnaire by the statistician, along with the limits of Cronbach alpha value scale measurements, the survey was available for administration on large scale. The questionnaire was administered to the willing participants, which included cancer hospitals in Hyderabad. A brief talk with respect to the survey and any elucidation in regards to any question was likewise done amid the meeting. The following questionnaire consisting of 10 questions was distributed among the oncologists in Hyderabad.

RESULTS

Out of medical oncologists (N=6) antioxidants were prescribed by 67% and not prescribed by 33%, Whereas among the radiation oncologists (N=24) antioxidants were prescribed by 67% and not prescribed by 25% of them (Figure 1). Among medical oncologists naturally available antioxidants were preferred by 75% where as 25% preferred commercially available antoxidants. Whereas 67% radiation oncologists prescribed naturally available antioxidants, 11 % preferred only commercially available forms of antioxidants and 22% preferred both natural and commercially available forms of antioxidants. A statistically significant $P<0.05$ shows that naturally available antioxidants were preferred by both medical & radiation oncologists. (Figure 2) 66.33% of medical oncologists believed that antioxidants would have palliative effect in cancer therapy whereas 33.33% did not believe that antioxidants would have palliative effect in cancer therapy. Whereas 66% radiation oncologists considered that antioxidants would not have palliative effect in cancer therapy and 34% of the them considered that antioxidants would have palliative effect in cancer therapy.(Figure 3) A statistically significant $P<0.05$ was obtained, where radiation oncologists did not believe that antioxidants have palliative effect in cancer therapy. While medical oncologists believe that antioxidants will have palliative effect in cancer therapy.

Analysis of survey on effects of antioxidants on complications during chemotherapy among medical oncologists

The percentage of medical oncologists who opined that antioxidants given along with cancer chemotherapy would reduce oral mucositis was 17%, xerostomia 0%, taste alteration 17%, neuropathy 17%, haematological complications 50%, immunological complications 83% , hair loss and revitalization of hair follicles 17%, hepatocellular and renal complications 33%, psychological disturbances 48% and hormonal imbalance was 0%, while remaining were not sure about the effect of antioxidants during chemotherapy. (Table 1) A statistical significance of $p < 0.05$ was obtained related to xerostomia and hormonal imbalance which strongly suggested that antioxidants cannot reduce chemotherapy induced side effects; Similar significance was obtained for enquiry into immunological complications suggested that prescription of antioxidants during chemotherapy would reduce burden.

Table 1. Percentages of medical oncologists opinion on effect of antioxidants on various complicationsrelated to chemotherapy

Medical oncologists	Yes	No	Ns	P value
Oral mucositis & ulcers	17%	50%	33%	>0.05
Xerostomia	0%	67%	33%	<0.05
Taste alteration	17%	50%	33%	>0.05
Neuropathy	17%	50%	33%	>0.05
Hematological complications	50%	33%	17%	>0.05
Immunological complication	83%	17%	0%	<0.05
Hair loss and promote revitalization of hair follicles	17%	50%	33%	>0.05
Hepatocellular and renal complication	33%	33%	33%	>0.05
Hormonal imbalance	0%	67%%	33%	<0.05

Table 2. Percentages of radiation oncologists opinion on effect of antioxidants on various complicationsrelated to radiotherapy

Radiation oncologists	YES	NO	NS	P value
Oral mucositis & Ulcers	66.66%	16.66%	16.66%	<0.05
Xerostomia	41.66%	33.33%	16.66%	>0.05
Taste alteration	41.66%	29.16%	29.16%	>0.05

Analysis of survey on effect of antioxidants on radiotherapy induced side effects among Radiation Oncologists

Among radiation oncologists, on the question of antioxidants during radiotherapy would reduce oral mucositis in 66%, xerostomia 41%, taste alteration 41% while some of them opinioned that antioxidants with radiotherapy will not reduce oral mucositis 16%, xerostomia 33%, Taste alteration 30% and osteoradionecrosis. (Table 2) A statistical significance of $P < 0.05$ obtained suggested that antioxidant would reduce radiotherapy induced oral mucositis. Among the medical oncologists 17% expressed that they confronted untoward drug interactions, when commercially available antioxidants were prescribed along with chemotherapeutic agents, whereas 66% of them expressed that they did not see such interactions. While, only 17% of the medical oncologists were not sure (Figure 4). 45% Radiation oncologists did not recommend antioxidants during radiotherapy and 16.33% recommended

antioxidants during radiotherapy. Where as 38.66 % were not sure of advocating antioxidants. Among 16.33% Radiation oncologists, 30% recommended antioxidants before radiotherapy whereas 58% recommended to start antioxidants after radiotherapy with a significant $P < 0.05$ whereas 12% were not sure of the answer. (Figure 5) 83 % medical oncologists and 88% radiation oncologists did not come across any complications with long term prescription of antioxidants ($P < 0.05$). Whereas, 17% medical oncologist and 12% radiation oncologists were not sure. 83% of medical oncologists and 92% of radiation oncologists did not believe that antioxidants could prevent recurrence of cancer ($P < 0.05$).

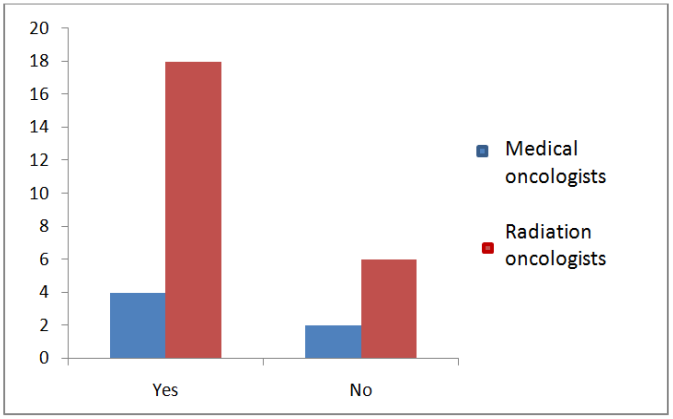

Figure 1. Prescription of antioxidants for the patients diagnosed withhead and neck cancer by oncologists

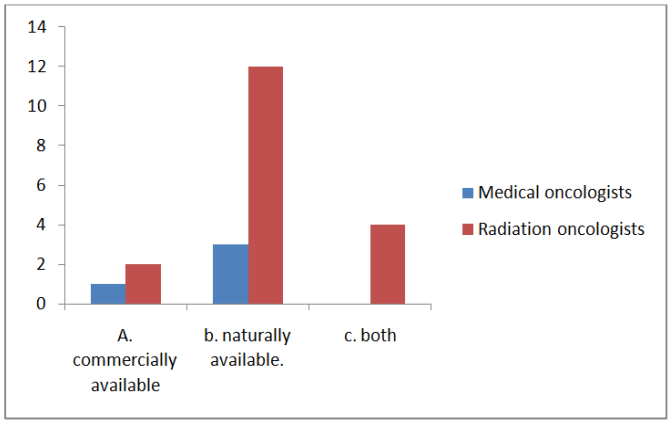

Figure 2. Oncologists opinion on comercially and naturally available antioxidants and their palliative effect in head and neck cancer therapy

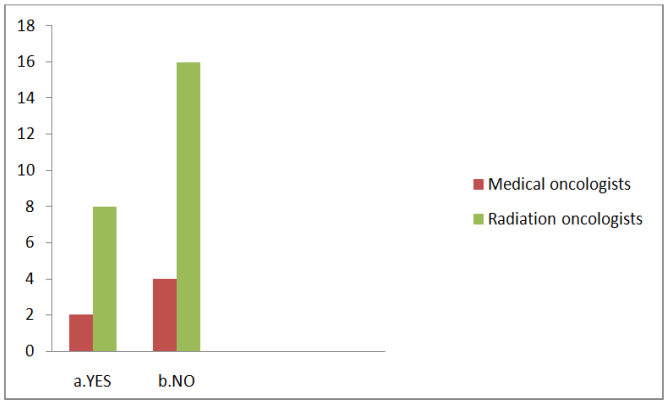

Figure 3. Oncologists opinion on antioxidants and palliative effect in head and neck cancer therapy

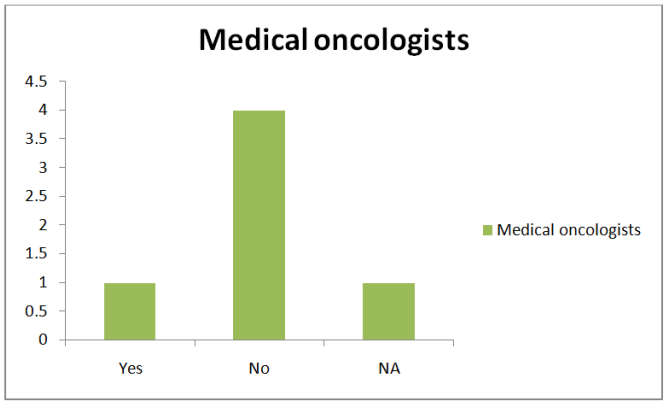

Figure 4. Medical Oncologists opinion regarding the untoward drug interactions of antioxidants with chemotherapeutic agents

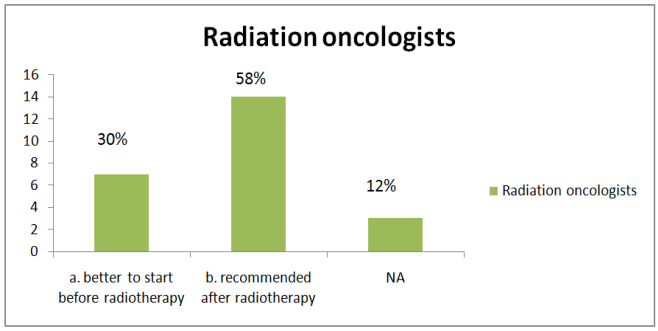

Figure 5. Radiation oncologists opinion about time of administration of antioxidants and radiotherapy

DISCUSSION

Antioxidants counteract free radicals and prevent them from causing tissue and organ damage. They function through a variety of mechanisms; as preventive agents that scavenge the free radicals, hence called as radical scavenging agents that inhibit chain initiation and/or propagation, de novo enzymes that repair and reconstitute cell membranes, and as adaptive agents that generate appropriate antioxidant enzymes and transfer them to the necessary site of action. (Norman *et al.*, 2003) Radiotherapy and numerous chemotherapy drugs produce free radicals; Some vitamins like vitamins C and E complex with free radicals thereby preventing oxidative harm. And there is a high likelihood that such a coupling might diminish the viability of cytotoxic treatment. (Bairati *et al.*, 2005) Some oncologists (medical or radiation) are of a view that antioxidants are capable of diminishing the effectiveness of chemo- and radiation therapy. However, there is some amount of variation between the medical and radiation oncologists as to whether these antioxidants play a positive or negative role. (Moss, 2007) One hypothesis states that the antioxidants help in preventing and repairing the healthy cells which are damaged due to the chemotherapy or radiation therapy and can result in less severe side effects. Also, the role of antioxidants in directly inducing apoptosis in malignant cells and thereby enhancing the antitumor effect of chemotherapy has been well documented both invivo and invitro. On the contrary, another hypothesis states that the antioxidants may directly act against the conventional cancer modalities by lowering the oxidative damage and hence repairing and protecting the cells. However, it must be noted that many cancer treatments act by destroying the cancer by inducing oxidative damage. (Lobo *et al.*, 2010;

Mut-Salud *et al*., 2016) Certain in vitro studies conducted by Teicher BA *et al*, Chinery R, Prasad KN, Rutz HP, Koch CJ have reported that the effectiveness of chemotherapy and radiotherapy can be enhanced by vitamins A, C, and E, as well as carotenoids. (Teicher *et al*., 1994; Chinery *et al*., 1997; Prasad *et al*., 1979; Rutz and Little, 1989; Koch and Biaglow, 1978) With such inclonclusive evidence against their use, some oncologists prefer not to prescribe such formulations during treatment. (Bairati *et al*., 2005)

In the present study naturally available antioxidants were more preferred by 75% of the oncologists (medical & radiation oncologists) with significant P value < 0.05. This was in correlation with the guidelines of recommendations by the American Institute for Cancer Research (AICR) that five or more servings of fruits and vegetables should be consumed daily to reduce the risk of certain cancers. The beneficial effects of fruits and vegetables for both healthy people and cancer survivors have sometimes been associated with the presence of various antioxidant micronutrients. (Bairati *et al*., 2006) Schmidinger *et al*. suggested that consuming antioxidants in whole foods vs. high-dose isolates may be unlikely to reach levels sufficiently high enough to interfere with treatment. (Schmidinger *et al*., 2000) Chemotherapeutic agents are toxic compounds that target rapidly proliferating cells, both malignant and normal. Thus, the effects of chemotherapy may result in oral complications which include: mucositis, pain, infection, hemorrhage, xerostomia, neurologic and nutritional problems. (Aslam *et al*., 2014) In the present study a significant percentage of medical oncologists believed that antioxidants would not reduce chemotherapy related side effects such as xerostomia and hormonal imbalance but may significantly reduce the immunological complications. While greater percentage of them believed that they will not reduce oral mucositis and ulcers, xerostomia, taste alteration, neuropathy and hairloss and hormonal imbalance but can reduce hematological complications. In contrary, Mills *et al*. (1988) in their study on Beta – carotene (250mg) supplementation with concurrent chemotherapy have observed a decrease in grade 3 or 4 mucositis (P <0.25) and Wadleigh *et al*. (1992) observed the reduction of mucositis in shorter period of time by using Vit.E oil (400mg, topical) during chemotherapy in patients with solid tumors and leukemia. It was hypothesized that the defensive impact of vitamin C may be much more noteworthy for tumors. But the data obtained from invitro studies were extrapolated to human cells. (Simone *et al*., 2007) This was in negative correlation with a study done by *Conklin K* where in oxidative stress induced by chemotherapy itself may actually hinder the effects of chemotherapy and the addition of antioxidants may actually help chemotherapy to work in a more natural, non-inflammatory way (i.e. through apoptosis rather than necrosis). (Conklin, 2004) However, this invitro sample cannot be corroborated to human trails on ascorbic acid usage during cancer treatment.

In accordance with our study, Falsaperla *et al* found decreased neutropenia in patients who took ellagic acid (180 mg PO) a non dietary antioxidant during chemotherapy in patients with hormone refractory prostate. (Falsaperla *et al*., 2005) In contrary, Lissoni *et al* in his study on supplementation of melatonin 20mg PO in patients undergoing chemotherapy for metastatic non- small cell lung cancer found significant decrease in neurotoxicity (P < 0.01), thrombocytopenia (P< 0.01), asthenia (P < 0.05) and also increased tumor regression rate in antioxidant patients. (Lissoni *et al*., 2003; Lissoni *et al*., 1999) Schmidinger *et al*, found satistically significant decrease in hematologic toxicity in patients on Glutathione (5g IV) during chemotherapy for head and neck cancer and non small cell lung cancer which was in accordance with the present study, as 50% 0f the medical oncologists observed reduced hematologic toxicity on administration of antioxidants during chemotherapy. (Schmidinger *et al*., 2000) A study by Cascium SCV *et al*, documented decreased neuropathy in antioxidant group (Glutathione 1500 mg/m^2, IV) after 12 cycles of chemotherapy in patients with advanced colorectal carcinoma. (Cascinu *et al*., 1995) The definitive treatment for Head and neck cancer is radiotherapy which is associated with adverse effects on normal tissue. Acute side effects frequently seen are mucositis, dysphagia, hoarseness, erythema, and desquamation of the skin, whereas, chronic complications are chiefly because of chronic injury to vasculature, salivary glands, mucosa, connective tissue, and bone. (Dirix *et al*., 2006) In the present study a significant percentage of radiation oncologists believed that antioxidants would reduce radiotherapy related acute side effects like oral mucositis and ulcerations with a significant p value of < 0.05. While, almost equal number of radiation oncologists had an opinion that antioxidants may or may not reduce radiotherapy induced xerostomia. And, about 41% percentage of radiation oncologists opined that antioxidant supplementation would not correct the taste alterations caused by radiation therapy.

In a study conducted by Ferreria *et al*, the patients undergoing radiotherapy for head and neck cancer were subjected to a double-blind, placebo-controlled RCTs by administering vitamin E. And, he concluded that, mucositis was significantly less in patients receiving α -tocopherol compared to patients receiving placebo (p = .038). (Ferreira *et al*., 2004) In a study by Babaee *et al*, which determined the antioxidant effect of Calendula officinalis (marigold flowers) flowers extract mouthwash as oral gel on radiation-induced oropharyngeal mucositis (OM) in patients with head-and-neck cancer. It was also demonstrated that Calendula extract gel was found to be effective on decreasing the intensity of radiotherapy- induced OM during the treatment and antioxidant capacity may be partly responsible for the effect, this is in accordance with the opinion of greater percentage of radiation oncologists in this study. (Babaee *et al*., 2013) The majority of radiation oncologists acceptance with the statement that antioxidants were helpful in reducing oral mucositis was in positive correlation with a similar study by Lalla *et al*., in which an antioxidant RK-0202 (RxKinetix) consisted of the antioxidant N-acetylcysteine for topical application in the oral cavity. In a placebo-controlled phase II trial in patients with head and neck cancer, this agent significantly reduced the incidence of severe oral mucositis up to doses of 50 Gyradiation therapy. (Lalla *et al*., 2008) Youssef Al-Tonbary *et al*, demonstrated the diminished treatment related toxicity with low levels of malondialdehyde (MDA) and high glutathione peroxidase (Glu.PX) antioxidant enzyme as well as reduced complications such as hepatoxicity and platelet related defects. The study results concluded that vitamin E and NAC (N-acetyl cysteine) in combination was effective as adjuvant therapy in peadiatric group suffering from ALL in reducing the chemo/radiotherapy related toxicities during the initial stages of treatment. (Al-Tonbary *et al*., 2009) A survey conducted by Simone CB *et al* reviewed the literature from 1996 through 2003 on the supplemental use of antioxidants (over the counter supplements like β-carotene; vitamins A, C, E, D and K; B vitamins;

selenium; cysteine; and glutathione, as single agents or in combination) with chemotherapy and radiotherapy and have concluded that these non-prescription antioxidants and other nutrients do not interfere with cancer chemotherapy or radiotherapy." (Simone *et al*., 2007)

In the present study prescription of antioxidants during radiotherapy was recommended by 50% of the radiation oncologists. The reasons could have been attributed to findings from a study conducted by Bairati *et al*. in which 540 head and neck cancer patients undergoing radiotherapy were included and were randomly assigned to receive concurrently either alpha-tocopherol (400 IU daily) with or without beta carotene (30 mg daily) vs placebo. They concluded that those who received both antioxidants had a statistically significant reduction in severe, acute side effects. This study also showed an insignificant increase in cancer recurrence rate among patients treated with radiation and supplemental antioxidants. This risk was only limited to the patients who smoked during cancer radiationtherapy, and was in contrary to the present study in which 83% of medical oncologists and 92% of radiation oncologists opined that antioxidants will not prevent recurrence of cancer. (Bairati *et al*., 2005; Bairati *et al*., 2005) Chitra and Shyamaladevi observed an increase in the activities of antioxidant enzymes in oral cancer patients who were supplemented with alpha-tocopherol during radiotherapy, and found a significant decrease in the malondialdehyde levels as compared to radiation-treated oral cancer patients without alpha-tocopherol supplementation. (Chitra and Shyamaladevi, 2008) D' Andrea concludes that the use of antioxidants should be avoided during chemotherapy and radiotherapy, which was in correlation with this study where in the greater number of radiation oncologists did not recommend antioxidants during radiation therapy. (Chitra and Shyamaladevi, 2008) The biologic effect of antioxidants may be effected by the tumor microenvironment. For example, Beta carotene at elevated partial pressures of oxygen acts as a pro-oxidant. Because of the varying degree of tumor hypoxia either within the tumor or between different types of tumors, its effectiveness in scavenging free radicals and the antioxidant properties of beta carotene may be altered. Hence, the interaction between antioxidants and radiation therapy may be influenced by many factors, inclusive of tumor hypoxia and also the variable amount of antioxidants present in different tissues. (Margalit *et al*., 2012)

Conclusion

In an attempt to enhance the benefits of cancer therapy and to prevent or palliate the side effects associated with it, numerous cancer patients with or without the knowledge of the oncologist, use dietary supplements enriched with antioxidants either during or after the treatment. But the literature reports the diverging views on prescribing antioxidants to cancer patients who are undergoing conventional treatment. Potentially malignant conditions have served fair in assessing the cancer preventing role of antioxidants and there is quite a good availability of clinical data on the beneficial effects of antioxidants in premalignant conditions mainly in oral leukoplakia and OSMF. Our view on the utilization of corresponding antioxidant therapy with chemotherapy or radiation treatment can be outlined that, though the use of such antioxidant drugs in cancer patients were a common scenario in oncology practice, it would be prudent to prescribe them by weighing the risk vs benefit ratio as the literature has supported antioxidant usage during cancer therapy and also against its use. Better RCT's with proven efficacy, dosage and reduced tumor burden during their usage are warranted, given the current situation of their random prescription during chemo and radiotherapy of cancers. A proper protocol with the type, formulation and time of advocating the antioxidant i.e, before, during or after chemotherapy or radiation therapy is warranted. The use of nutritionally derived antioxidants is emphasized as they protect the normal cells from the oxidative damage caused by chemotherapeutic agents, they are shown not to interfere with the oncologic treatments and are also helpful in lowering the risk and the severity of comorbidities and ultimately improving the quality of life of these cancer patients. And the beneficial role of a number of commercially available antioxidants in their suprapharmacologic doses have to specifically studied for their therapeutic association with different cancer types. Though the clinical data is sparse with their effect on their overall benefit of the patient, they can well be included in natural form and further studies should be carried out to study the effect of antioxidants in radiochemotherapy in oral cancer.

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Questionnaire

1. Do you prescribe antioxidants for the patients undergoing treatment for head and neck cancer?

a. Yes	b. No

2. If yes, which antioxidants would you prefer to give?

a.Commercially available	b.Naturally Available.	c.Both	d.NS

3. Do you believe that antioxidants will have palliative effect in head and neck cancer therapy?

a. Yes	b. No	c.NS

4. In your opinion (medical oncologists), prescription of antioxidants as an adjuvant along with head and neck cancer chemotherapy can reduce

EFFECTS	Yes	No	NS
Oral mucositis & ulcers			
Xerostomia			
Taste alteration			
Neuropathy			
Haematological complications			
Immunological complication			
Hair loss and promote revitalization of hair follicles			
Hepatocellular & Renal complication			
Psychological disturbances			
Hormonal imbalance			

5. In your opinion (radiation oncologists), prescription of antioxidants as an adjuvant along with head and neck cancer radiotherapy can reduce

EFFECTS	Yes	No	NS
Oral mucositis & ulcers			
Xerostomia			
Taste alteration			

6. Have you come across any untoward drug interactions, when antioxidants are prescribed along with chemotherapeutic agents?

a. Yes	b. No	c.NS

7. In your opinion prescription of antioxidants during radiotherapy?

a.Not recommended	b. b.Highly recommended	c.NS

8. If recommended what is your opinion about time of administration of antioxidants and radiotherapy?

a.Better to start before radiotherapy	b.Recommended after radiotherapy	c.NS

9. Have you come across any complications with long term prescription of antioxidants?

a. Yes	b. No	c.NS

10. Do you believe that antioxidants prevent recurrence of cancer?

a. Yes	b. No	c.NS

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