The Egyptian Journal of Hospital Medicine (April 2024) Vol. 95, Page 1568- 1575

Impact of Vitamin D Supplementation on Head and Neck Cancer Patients Receiving Radiotherapy

Reham Ahmed Abdelaziz*, Enas Elkhouly, Amira Hegazy, Lama Kamal, Ashraf Abd El Ghany
Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Menoufia University, Egypt
***Corresponding author:** Reham Ahmed Abdelaziz, **Mobile:** (+20) 01006674714, **E-mail:** drrehamahmed85@gmail.com

ABSTRACT

Background: Vitamin D was found to have potent antioxidant effect and play an important role in activating the dendritic cells, macrophages, and monocytes, as well as stimulating DNA damage repair suggesting its role in reducing the incidence of radiation induced oral mucositis and other acute side effects.

Objective: To evaluate impact of vitamin D administration on radiation induced oral mucositis and other radiotherapy related toxicity and to assess its effect on response to treatment.

Patients and methods: This is a prospective case-control study conducted on sixty-one patients diagnosed as head and neck cancer that would receive radiotherapy either as definitive or adjuvant treatment at Clinical Oncology and Nuclear Medicine Department, Menoufia University. Two groups of patients; vitamin D group whom vitamin D was prescribed and control group without vitamin D. All the patients were examined clinically weekly after the start of radiotherapy for WHO mucositis score.

Results: Vitamin D supplementation reduced oral mucositis in head and neck cancer patients receiving radiotherapy with or without chemotherapy with significant improved oral mucositis in vitamin D arm, p value <0.001 in weeks two, three, four, five and six. Also, skin toxicity, taste changes and dysphagia were significantly better in vitamin D arm, p value at week one, two, three, four, five were 0.011, 0.041, 0.001, <0.001, 0.003 respectively, with higher incidence of xerostomia in vitamin D arm in weeks six and seven however no significant differences between two arms.

Conclusion: This study demonstrates that vitamin D administration had beneficial effect on reducing oral mucositis and other complications like skin toxicity, taste changes and dysphagia during radiotherapy treatment in head and neck cancer patients, it helps in the reduction of the chance of treatment interruption and improved response to radiation treatment.

Keywords: Oral mucositis, Radiotherapy, vitamin D.

INTRODUCTION

According to GLOBOCAN (2020), head and neck cancer (HNC) is the seventh most frequent malignancy in the globe, accounting for around 4.6% of all cancer deaths [(1)]. Radiation therapy is a cornerstone in the treatment of HNC patients [(2)].

The most severe non-hematological adverse effect of cancer treatment is radiation-induced oral mucositis, or "RIOM" [(3)].

According to certain publications, between 40% and 80% of patients with head and neck cancer who get radiation therapy for 6-7 weeks on average tend to develop RIOM [(4)]. Unplanned radiation therapy interruptions brought on by ulcerative mucositis and the acute side effects that follow have a severe influence on the course of treatment for many tumour types, with head and neck cancer appearing to be most affected [(5)].

Being a fat-soluble vitamin, vitamin D is mostly obtained via food and exposure to sunshine [(6)].

Studies in the past have demonstrated that the mucosa expresses vitamin D receptors. Low vitamin D levels are linked to heightened inflammation in the mucosal state and disruption of the mucosal tissue barrier because vitamin D reduces the expression and synthesis of various pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8, and increases the production of anti-inflammatory cytokines, such as IL-10 [(7,8)].

In addition, vitamin D protects endothelial cells from oxidative stress by regulating mitogen-activated protein kinase (MAPK) signalling and inhibiting phoho-38, p38 MAPK is critical for damage to occur, so it acts as a radioprotective agent against skin toxicity [(9,10)].

Furthermore, vitamin D had a potent antioxidant effect [(11)] and also had an important role in activating the dendritic cells, macrophages, and monocytes [(12)].

Another several studies, reported that vitamin D may protect against carcinogenesis through inhibiting survival signals and promoting apoptosis, as well as inhibiting cellular proliferation, and preventing tumor angiogenesis [(13)].

Hence, the aim of our study was to evaluate impact of vitamin D administration on radiation-induced oral mucositis and other radiotherapy related toxicity and to assess its effect on response to treatment.

PATIENTS AND METHODS

This prospective case-control study was carried out on 61 patients with newly diagnosed head and neck squamous cell carcinoma at Clinical Oncology and Nuclear Medicine Department, Menoufia University during the period between February 2022 and September 2022.

Received: 07/11/2023
Accepted: 07/01/2024

Histologically-proved head and neck squamous cell carcinoma, patients indicated to receive radiotherapy (either adjuvant or definitive therapy) according to NCCN and/or ESMO guidelines with or without chemotherapy and WHO performance status ≤ 2 were the ***inclusion criteria*** while patients with recurrent or metastatic head and neck squamous cell carcinoma, hyper calcemic patients, patients with any contraindications for radiation therapy and patients receiving any medications with drug interaction with vitamin D were ***excluded*** from the study.

METHOD

The studied patients were equally randomized (by simple random numbers generated by a computer) into two groups: group (1) (vitamin D arm) and group (2) (control arm).

Patients in **group (1)**, 30 patients, received vitamin D concomitantly with the radiation therapy. Initial serum vitamin D level was evaluated before treatment to calculate the doses of vitamin D either prophylactic or therapeutic based on reference range of vitamin D deficient < 20 ng/mL, insufficient between 21-29 ng/Ml and sufficient between 30-100 ng/Ml [(14)]. Adult patients with vitamin D deficiency were initially treated with 2,000-6,000 international units (IU) for 6-8 weeks. Patients who had vitamin D insufficiency received 400-2,000 IU cholecalciferol per day to achieve normal 25-hydroxyvitamin D levels. Patients with sufficient level of vitamin D received prophylactic doses of vitamin D. **Group (2)**, 31 patients, received radiation therapy without vitamin D.

Included patients underwent baseline evaluation; physical examination, and staging imaging; CT or MRI. Weekly, clinical examination during the course of radiotherapy with assessment of the grade of any toxicity including oral mucositis by using the Common Terminology Criteria for Adverse Events (CTCAE). Measurements were classified based on clinical characteristics, integrating subjective and objective measurements into grade 0: no oral mucositis, grade I: presence of soreness and erythema, grade II: presence of painful erythema and ulcerations that do not affect the patient's solid food intake, grade III: confluent ulceration that affects the solid food intake and requires a liquid diet, and grade IV: the patient requires parenteral nutrition and other radiotherapy-related toxicities. Skin dermatitis, xerostomia, taste changes, and dysphagia were also evaluated weekly according to (CTCAE) [(15)].

Evaluation of response to radiotherapy in studied patients were done 6 weeks later after treatment finished, by clinical examination and CTs or MRI and response to treatment was assessed according to revised RECIST guideline (version 1.1).

Ethical approval:

The Local Ethics Committee of the Faculty of Medicine at Menoufia University authorised the study design (Approval number 2/2022ONCO46). Confidentiality and personal privacy were observed at all stages of the investigation. Each participant received a full summary of the study's aims prior to completing an informed consent form. The Helsinki Declaration was observed at all stages of the study.

Statistical analysis

The data were coded, processed, and analysed with SPSS version 22 for Windows®. The Shapiro Wilk test was used to determine the normal distribution of the data. The qualitative data were reported as frequencies and relative percentages. The χ^2 test and Fisher exact test were used to compare qualitative variables. The quantitative data were presented as mean ± SD, median, and range. The independent samples t-test was used to compare two independently distributed sets of variables (parametric data). A significant p-value was defined as being equal to or less than 0.05.

RESULTS

Cancer larynx was the dominant diagnosis in the study represented (42.6%) of all diagnoses. According to TNM staging, most common stage was 1Va. There was no significant difference regarding demographic data between the two groups as regard age, sex, smoking history, PS, co-morbidities and in treatment data of the studied cases (does, duration of radiotherapy and chemotherapy used) **(Table 1).**

Table (1): Demographic, clinicopathological features, and treatment data of both studied groups

Variables		Vitamin D arm (n = 30)		Control arm (n = 31)		Test of sign. (χ^2)	P value
		No.	%	No.	%		
Age	Mean ±SD	57.12±11.79		56.87±13.4		t=0.081	0.936
	Median (range)	58 (36-83)		56 (21-84)			
Gender	Male	22	73.3	21	67.7	0.229	0.632
	Female	8	26.7	10	32.3		
Smoking history	yes	13	43.3	23	74.2	2.075	0.15
	no	17	56.7	8	25.8		
PS	**1**	28	93.3	29	93.5	FE	1
	2	2	6.7	2	6.5		
Comorbidities	yes	24	80	23	74.2	0.291	0.590
	no	6	20	8	25.8		
Site of the disease	Nasopharynx	4	13.3	2	6.5	4.605	0.595
	Oropharynx	2	6.7	2	6.5		
	Oral cavity	9	30	6	19.4		
	Hypopharynx	0	0	3	9.7		
	Larynx	12	40	14	45.2		
	Maxillary sinus	2	6.7	3	9.7		
TNM stage	I	5	16.7	5	16.1	0.042	0.998
	II	9	29.9	9	29		
	III	8	26.7	10	32.3		
	IVa	8	26.7	7	22.6		
Treatment received	Radiotherapy alone	13	43.3	14	45.2	0.021	0.886
	chemoradiotherapy	17	56.7	17	54.8		
Radiotherapy dose	Mean	65.17±8.57		66.77±4.66		t =0.913	0.365
	Median (Range)	65 (55-70)		66 (55-74)			
Number of fractions	Mean ±SD	31.73±4.64		32.23±4.33		t =0.428	0.749
	Median (Range)	31 (20-70)		32 (20-37)			
Duration of radiotherapy (weeks)	Mean ±SD	6.33±1.06		6.42±1.03		t =0.322	0.670
	Median (Range)	6.1 (4-7)		6.5 (4-8)			
Concurrent chemotherapy and targeted agent	**None**	13	43.3	14	45.2	0.021	0.990
	cisplatin	16	53.3	16	51.6		
	others	1	3.3	1	3.2		

$\chi 2$ =Chi-square test; FE: Fisher's exact test, t = Student's t test.

There was significant reduction in the incidence and the grades of OM in the vitamin D arm than control arm in weeks two, three, four, five and six. At week seven, higher number of the patients developed OM in control arm than vitamin D arm with no patients developed grade IV OM in vitamin D arm, nevertheless the difference was statistically insignificant **(Table 2)**.

Table (2): Comparison between studied groups regarding development oral mucositis (OM)

Grades	Vitamin D arm		Control arm		Test of sign. (χ^2)	P value
	No.	%	No.	%		
Week 1	No.=30		No.=31			
No toxicity	26	86.67	25	80.65	0.403	0.525
Grade 1	4	13.33	6	19.35		
Week 2	No.=30		No.=31			
No toxicity	24	80.0	0	0.0	44.195	<0.001**
Grade 1	6	20.0	14	45.2		
Grade 2	0	0.0	14	45.2		
Grade 3	0	0.0	3	9.7		
Week 3	No.=30		No.=31			
No toxicity	12	40.0	0	0.0	38.667	<0.001**
Grade 1	14	46.7	3	9.7		
Grade 2	4	13.3	14	45.2		
Grade 3	0	0.0	13	41.9		
Grade 4	0	0.0	1	3.2		
Week 4	No.=29		No.=30			
No toxicity	6	20.7	0	0.0	35.412	<0.001**
Grade 1	16	55.2	2	6.7		
Grade 2	7	24.1	10	33.3		
Grade 3	0	0.0	15	50.0		
Grade 4	0	0.0	3	10.0		
Week 5	No.=29		No.=28			
No toxicity	4	13.8	0	0.0	34.281	<0.001**
Grade 1	14	48.3	0	0.0		
Grade 2	10	34.5	9	32.1		
Grade 3	1	3.4	16	57.1		
Grade 4	0	0.0	3	10.7		
Week 6	No.=28		No.=28			
Grade 1	15	53.6	0	0.0	29.166	<0.001**
Grade 2	10	35.7	7	25.0		
Grade 3	3	10.7	19	67.9		
Grade 4	0	0.0	2	7.1		
Week 7	No.=19		No.=22			
No toxicity	0	0.0	1	4.5	8.131	0.087
Grade 1	7	36.8	1	4.5		
Grade 2	8	42.1	11	50.0		
Grade 3	4	21.1	8	36.4		
Grade 4	0	0.0	1	4.5		

χ^2 =Chi-square test, **: Statistically highly significant.

Regarding to other toxicities including skin toxicity, taste changes and dysphagia, there were significant improvement in the incidence of these toxicities in vitamin D arm than in control arm at week one, two, three, four, five. There was higher incidence of xerostomia in vitamin D arm in weeks six and seven, however no significant differences were found between two arms **(Table 3).**

Table (3): Comparison between studied groups regarding other complication

Grades	Vitamin D arm		Control arm		Test of significance (X^2)	P value
	No.	%	No.	%		
Week 1	No.=30		No.=31			
No toxicity	30	100.0	25	80.6	FE	0.011*
Taste changes	0	0.0	6	19.4		
Week 2	No.=30		No.=31			
No toxicity	27	90.0	20	64.5	FE	0.041*
Taste changes	3	10.0	10	32.3		
Dysphagia and Dysgeusia	0	0.0	1	3.2		
Week 3	No.=30		No.=31			
No toxicity	23	76.7	10	32.3	16.520	0.001**
Taste changes	6	20.0	7	22.6		
Xerostomia	0	0.0	1	3.2		
Skin Toxicity	0	0.0	2	6.5		
Dysphagia and Dysgeusia	1	3.3	11	35.5		
Week 4	No.=30		No.=31			
No toxicity	21	70.0	10	32.3	18.292	<0.001**
Taste changes	6	20.0	2	6.5		
Xerostomia	0	0.0	1	3.2		
Skin Toxicity	0	0.0	6	19.4		
Dysphagia and Dysgeusia	3	10.0	12	38.7		
Week 5	No.=29		No.=31			
No toxicity	20	69.0	11	35.5	16.195	0.003*
Taste changes	4	13.8	2	6.5		
Xerostomia	2	6.9	0	0.0		
Skin Toxicity	1	3.4	10	32.3		
Dysphagia and Dysgeusia	2	6.9	8	25.8		
Week 6	No.=28		No.=13			
Taste changes	5	17.9	0	0.0	5.830	0.120
Xerostomia	4	14.3	0	0.0		
Skin Toxicity	8	28.6	7	53.8		
Dysphagia and Dysgeusia	11	39.3	6	46.2		
Week 7	No.=17		No.=20			
Taste changes	3	17.6	1	5.0	7.616	0.055
Xerostomia	4	23.5	0	0.0		
Skin Toxicity	5	29.4	10	50.0		
Dysphagia and Dysgeusia	5	29.4	9	45.0		

χ^2 =Chi-square test; FE: Fisher's exact test, *: Statistically significant, **: Statistically highly significant

As regard to response to treatment, 22 patients in vitamin D arm and 23 patients in control arm were available for response assessment (they had gross diseases before initiation of treatment). Significant better response was found in vitamin D arm than in control arm **(Table 4 and Figure 1)**.

Interruption of treatment was insignificantly more frequent at control arm, five patients (16.1%) had interrupted treatment in control arm due to oral mucositis and other toxicities versus no interruption of treatment in intervention arm **(Table 4 and figure 2).**

Table (4) Comparison between studied groups regarding response to treatment and interruption of treatment:

Grades	Vitamin D arm		Control arm		Test of significance (χ^2)	P value
	No.	%	No.	%		
	No.=22		No.=23			
Complete response	12	54.5	5	21.7	χ^2 = 8.3643.	0.039
Partial response	8	36.5	8	34.7		
Stationary disease	1	4.5	7	30.4		
Disease progression	1	4.5	3	13.2		
Treatment interruption	No.=30		No.=31			
No	30	100	26	38.9	FE	0.053
Yes	0	0	5	16.1		

χ^2 =Chi-square test; FE: Fisher's exact test.

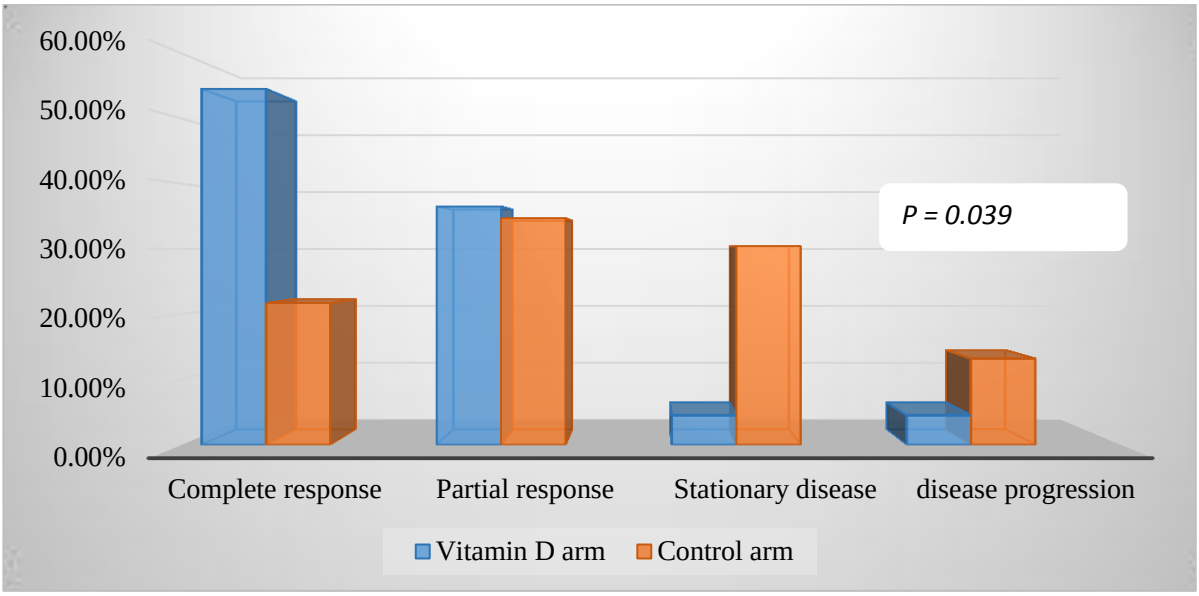

Figure (1): Response to treatment in both studied arms.

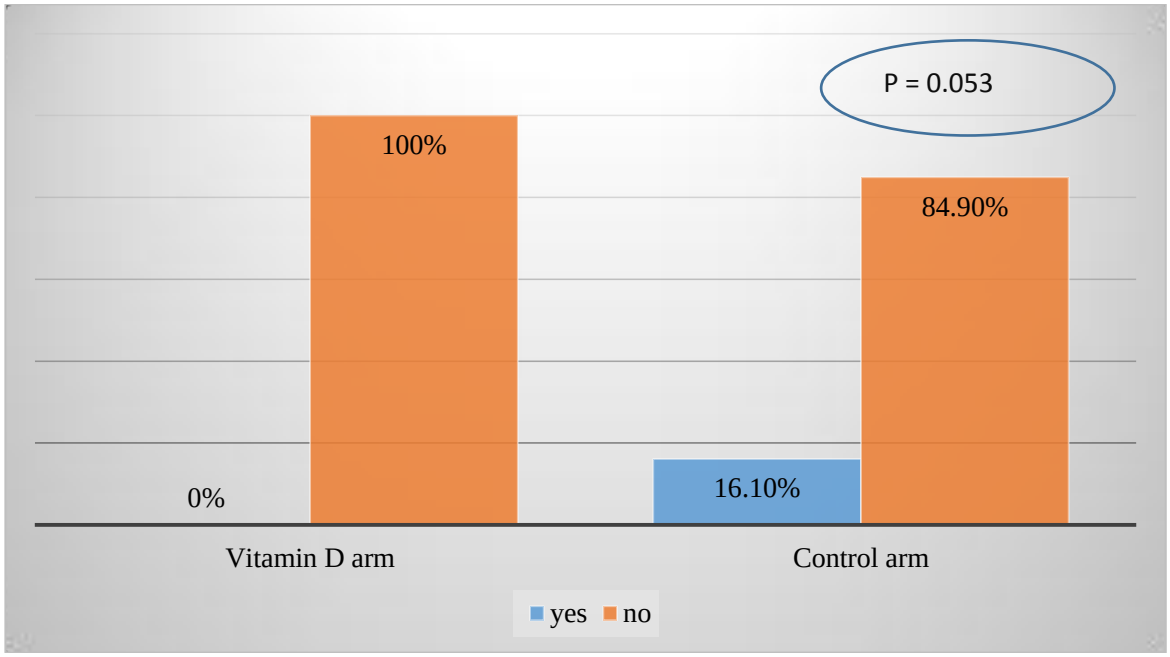

Figure (2): Treatment interruption in both studied arms.

DISCUSSION

Radiotherapy represents a gold standard treatment option in patients with HNC either as definitive therapy or adjuvant treatment with or without chemotherapy. However, it commonly results in systemic infection, dehydration, malnourishment, pain, odynodysphagia, dysgeusia, ulceration of the oral cavity, and poor quality of life and survival due to dosage reduction or medication termination [16].

In the present study there was no significant differences between the two groups regarding demographic, clinicopathological features and treatment data indicating homogenous patients' characteristics of both groups. In the current study, vitamin D administration significantly improved oral mucositis in HNC patients receiving radiotherapy either alone or concurrently with chemotherapy on weekly assessment of patients**.**

Similarly, in the study by **Anand *et al.*** [17], they showed that systemic vitamin D supplementation significantly improved oral mucositis. However, vitamin D was given to all of the patients in the study at a fixed dose of 1000 IU BD per day for three months without any baseline measurements or adjustments to the dose for prophylactic or therapeutic purposes.

In the current study patients were classified according to initial serum of vitamin D into vitamin D deficient, insufficient and sufficient and the vitamin D was prescribed either therapeutic or prophylactic. Furthermore, we used higher dose of radiotherapy that ranged from 55 to 70 Gray with mean of 61 Gray versus 46 Gray in 23 fractions in the study of **Anand *et al.*** [17].

Also, the current study's findings were consistent with those of **Nejatinamini *et al.*** [18]**,** who found that 52% of patients developed moderate to severe mucositis (score 2 or above) at some time during therapy and had lower baseline dietary intakes of vitamins D, E, folate, and B12.

Bakr *et al.* [19] examined topical vitamin D, they found reduction in the severity of oral mucositis at the first assessment after three weeks. There was no significant difference between the patients who received topical vitamin D and the control group (p =0.690) despite the minor indications of OM (WHO grade <2). The potential explanation for the observed decrease in OM might stem from vitamin D's ability to downregulate the expression and synthesis of many pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8, while simultaneously promoting the production of anti-inflammatory cytokines, such as IL-10 [19]**.**

The current study found that vitamin D supplementation had a substantial impact on reducing other radiotherapy related side effects like skin toxicity, taste changes and dysphagia during whole period of radiotherapy and these results were explained by **Hall *et al.*** [10], who showed that vitamin D acts as anti-inflammatory by protecting endothelial cells from oxidative stress, so it acts as a radioprotective agent against skin toxicity during radiotherapy. Also**, Anand *et al.*** [17] showed the impact of vitamin D supplementation on significant improving the problems of chemoradiation-induced toxicity, xerostomia, pain and odynophagia.

The results obtained from the current study and the previous mentioned studies revealed the efficacy of vitamin D in minimising the detrimental effects of radiation on oral mucosa, most likely via the robust antioxidant and immunomodulatory properties of vitamin D, allowing for continuous cancer therapy as reported by **Mokhtari *et al.*** [11] **and Wimalawansa** [20]**.**

In this study interruption of treatment occurred only in five patients in the control arm versus no patients in the intervention arm without significant difference, which met with **Anand *et al.*** [17] who showed that vitamin D also improved response to treatment indirectly by enabling the patient to complete the full treatment regimen and improving patients' ability to tolerate treatment.

In the present study**,** treatment response was evaluated after six weeks of finishing radiotherapy and we found a better response to treatment in the vitamin D arm. Our results are in line with **Yu *et al.*** [21] who explained that vitamin D may act as a radiosensitizer by promoting tumour death and inhibiting angiogenesis. But this is in contrast to **Dudding *et al.*** [22] who did not support the observational connection between vitamin D and the incidence of oral cancer. However, the effect of vitamin D on the advancement of oral cancer was not examined.

CONCLUSION

This study demonstrates that vitamin D supplement, either therapeutically or prophylactically, significantly improved oral mucositis and other radiotherapy related toxicity like skin toxicity, taste changes, xerostomia and dysphagia in head and neck cancer patients. Vitamin D also showed a promising effect in reducing interruption of treatment and hence improving response to radiotherapy.

- **Conflict of interest:** None declared.
- **Fund:** Non-fundable.

REFRENCES

1. **Sung H, Ferlay J, Siegel R (2021):** Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer Journal for Clinicians, 71(3): 209-249.
2. **Moslemi D, Nokhandani A, Otaghsaraei M *et al.* (2016):** Management of chemo/radiation-induced oral mucositis in patients with head and neck cancer: A review of the current literature. Radiotherapy and Oncology, 120(1): 13–20.
3. **Muanza T, Cotrim A, Mcauliffe M *et al.* (2005):** Evaluation of radiation-induced oral mucositis by

optical coherence tomography. Clin Cancer Res., 11(14):5121-7.

4. **Pandey P, Prakashtikku A, Mishra S *et al.* (2019):** Oral mucosal status of children with cancer undergoing treatment at a tertiary health care facility in Lucknow. India, 6691: 2260– 2265.
5. **Bese N, Hendry J, Jeremic B (2007):** Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. Int J Radiat Oncol Biol Phys., 68: 654–661.
6. **Menshawey E, Menshawey R, Nabeh O (2021):** Shedding light on vitamin D: the shared mechanistic and pathophysiological role between hypovitaminosis D and COVID-19 risk factors and complications. Inflammopharmacology, 29(4): 1017–1031.
7. **Sun J (2010):** Vitamin D and mucosal immune function. Current Opinion in Gastroenterology, 26(6): 591-595.
8. **Li Y, Chen Y, Du J (2015):** Critical roles of intestinal epithelial vitamin D receptor signaling in controlling gut mucosal inflammation. The Journal of Steroid Biochemistry and Molecular Biology, 148: 179-183.
9. **Anoopkumar-Dukie S, Conere T, Sisk G *et al.* (2009):** Mitochondrial modulation of oxygen-dependent radiosensitivity in some human tumour cell lines. Br J Radiol., 82:847–854.
10. **Hall S, Rudrawar S, Zunk M *et al.* (2016):** Protection against radiotherapy induced toxicity. Antioxidants, 5(3): 22. https://doi.org/10.3390/ANTIOX5030022.
11. **Mokhtari Z, Hekmatdoost Z, Nourian M (2017):** Antioxidant efficacy of vitamin D. Journal of Parathyroid Disease, 5(1): 11-16.
12. **Barragan M, Good M, Kolls J (2015):** Regulation of dendritic cell function by vitamin D. Nutrients, 7(9): 8127–8151.
13. **Umar M, Sastry K, Chouchane A (2018):** Role of vitamin D beyond the skeletal function: A review of the molecular and clinical studies. International Journal of Molecular Sciences, 19(6): 1–28.
14. **Patel R, Bazydlo L, Brown S *et al.* (2021):** Vitamin D replacement in adults: Current strategies in clinical management. Practical Gastroenterology, 21: 16-31.
15. **Sroussi H, Epstein J, Bensadoun R *et al.* (2017):** Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer Medicine, 6(12): 2918–2931.
16. **Münstedt K, Momm F, Hübner J (2019):** Honey in the management of side effects of radiotherapy- or radio/chemotherapy-induced oral mucositis. A systematic review. Complementary Therapies in Clinical Practice, 34: 145–152.
17. **Anand A, Singh S, Sonkar A *et al.* (2017):** Expression of vitamin D receptor and vitamin D status in patients with oral neoplasms and effect of vitamin D supplementation on quality of life in advanced cancer treatment. Contemporary Oncology, 21(2): 145–151.
18. **Nejatinamini S, Debenham B, Clugston R *et al.* (2018):** Poor vitamin status is associated with skeletal muscle loss and mucositis in head and neck cancer patients. Nutrients, 10(9):1236. https://doi.org/10.3390/nu10091236
19. **Bakr I, Zaki A, El-Moslemany R *et al.* (2021):** Vitamin D oral gel for prevention of radiation-induced oral mucositis: A randomized clinical trial. Oral Diseases, 27(5): 1197–1204.
20. **Wimalawansa S (2019):** Vitamin D deficiency: Effects on oxidative stress, epigenetics, gene regulation, and aging. Biology, 8(2): 30. https://doi.org/ 10.3390/biology8020030.
21. **Yu X, Liu B, Zhang N *et al.* (2021):** Immune response: A missed opportunity between vitamin D and radiotherapy. Frontiers in Cell and Developmental Biology, 9: 913. https://doi.org/10.3389/ fcell.2021.646981.
22. **Dudding T, Johansson M, Thomas S *et al.* (2018):** Assessing the causal association between 25-hydroxyvitamin D and the risk of oral and oropharyngeal cancer using Mendelian randomization. International Journal of Cancer, 143(5): 1029–1036.