ORIGINAL ARTICLE

CONTENTS

Radiation-induced mucositis and salivary EGF levels in patients with head and neck cancer

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ABSTRACT

Aim: The present study aims to investigate the correlation between the concentration of salivary epidermal growth factor and the development of radiation-induced mucositis in patients diagnosed with head and neck cancer.

Materials and Methods: A cross-sectional study examined radiotherapy-treated head and neck cancer patients. Saliva samples were collected before radiation treatment, as well as at two weeks and four weeks after starting treatment. The epidermal growth factor levels in saliva samples were measured using enzyme-linked immunosorbent assay (ELISA).

Results: After two and four weeks of radiation, EGF expressions were considerably greater than those in the control group. The optimal cut-off EGF for prediction of oral mucositis after radiotherapy was 502.1 pg/ml.

Conclusions: epidermal growth factor level may affect radiation-induced mucosal healing. In patients receiving regular daily fractions of radiation, higher EGF concentrations reduced the probability of mucositis occurrence. Oral mucositis has decreased compared to prior trials using older radiation delivery technologies.

KEY WORDS: mucositis, epidermal growth factor, radiotherapy, head and neck neoplasms

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ABBREVIATIONS

EGF: Epidermal Growth Factor
RT: Radiation Therapy
EBRT: External Beam Radiation Therapy
VMAT : Volumetric Modulated Arc Therapy
ROC: Re1ceiver Operating Characteristic
IMRT: Intensity Modulated Radiation Therapy

INTRODUCTION

Oral mucositis is a term used to describe lesions that cause painful, erythematous, and ulcerative changes in the mouth and is frequently a side effect of antineoplastic therapy for head and neck cancer treatment [1-2] accompanied by notable discomfort, odynodysphagia (painful swallowing), dysgeusia (altered taste perception), dehydration, malnutrition, and a deterioration in speaking ability, overall oral health, and quality of life [3]. Almost all patients who undergo radiation therapy to the head and neck experience some degree of oral mucositis [4]. The incidence of head and neck cancer is on increasing numbers, primarily driven by an increase in oropharyngeal cancers. This is in contrast to a decline in the occurrence of head and neck cancer originating from other specific locations [5]. Among individuals who do not use tobacco or alcohol, HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) is more common than HPV-negative OPSCC. However, patients with HPV-positive OPSCC still have a significant history of tobacco and alcohol use, which is linked to poorer outcomes. The global prevalence of HPV-positive oropharyngeal squamous cell carcinomas (OPSCCs) was reported to be 33% in 2021. However, the prevalence varies significantly across different geographical regions, with estimations ranging from 0% in southern India to 85% in Lebanon [6]. According to a five-phase model of mucositis pathogenesis, the initial cause and stimulus for the inflammatory process is the microvascular damage inflicted upon rapidly dividing basal epithelial cells during radiation and chemotherapy. This damage leads to the generation and release of free oxygen radicals, which subsequently activate var-

ious cytokines, including tumor necrosis factor-alpha primarily produced by macrophages, as well as interleukin-1 and -6. The occurrence of ulcers in the mucosa serves as a foundation for the establishment of bacterial microflora, thereby giving rise to subsequent infections. The final stage, known as healing, is distinguished by the proliferation of epithelial cells, the differentiation of tissues, and the restoration of epithelial integrity [7-8]. Radiation-induced damage to basal epithelial cells begins to occur at cumulative doses of 10-15 Gy, typically becoming evident after approximately 10 days. The seriousness of this condition becomes prominent at 30 Gy, lasting for several weeks or possibly even months [9]. The polypeptide known as epidermal growth factor (EGF) consists of 53 amino acid residues and plays a significant role in the control of cell proliferation. The effects of EGF are mediated through the binding of EGF to the EGF receptor, which is located on the plasma membrane of target cells [10]. The process of binding to epidermal growth factor (EGF) receptors triggers a cascade of biochemical reactions, ultimately leading to the transmission of a signal that induces modifications in gene regulation [11]. Epidermal growth factor is found in the oral environment as a result of its synthesis largely taking place in the salivary glands of humans, even though the kidneys are responsible for the systemic release of EGF. The quantity of EGF present in human saliva is equivalent to 1 ng/ml. This suggests that the administration of EGF may potentially contribute to the maintenance of oral mucosal integrity and expedite the process of wound healing [12-13]. It has been suggested that a decrease in salivary EGF levels may impair the oral mucosa's ability to heal following injury or to withstand injury [14-15]. Salivary EGF has been observed to be detectable in individuals suffering from oral inflammation as well as those diagnosed with head and neck carcinoma. The previous investigations observed a decline in overall epidermal growth factor (EGF) levels in the combined saliva of individuals undergoing radiation therapy (RT) for head and neck carcinoma [16-17]. The determination of plasma parameters is a crucial technique in clinical routine diagnostics, while the utilization of other bodily fluids as supplementary sources is comparatively limited. The collection of saliva specimens is a convenient and straightforward process, characterized by its rapidity, noninvasiveness, minimal stress on the individual, and relatively low cost. In contrast, the acquisition of blood samples necessitates the use of sterile equipment and supplies [18]. The presence of mucositis and other complications imposes a greater economic burden due to the heightened susceptibility to infection and the subsequent rise in morbidity and mortality rates. Furthermore, it serves as a primary factor contributing to the reduction of therapeutic doses, limitations on the implementation of optimal cancer therapy protocols, and premature discontinuation of treatment for chemoradiotherapy. These factors have the potential to directly reduce the rates of successful treatment and negatively influence the survival rate and the quality of life experienced by patients [19], therefore, developing instruments for healthcare professionals to evaluate the risk of oral mucositis through analyzing EGF levels, so enabling prompt implementation of intervention methods. A more comprehensive comprehension of the biological mechanisms through which EGF levels impact the progression of oral mucositis is required. The complete elucidation of the precise causal pathways and interactions with other molecular factors is still pending. A knowledge gap exists with respect to the efficacy of interventions that rely on the monitoring of EGF levels. The potential impact of modifying treatment regimens for patients with low EGF levels on ameliorating the severity of mucositis or improving outcomes remains uncertain. The objective of this study is to determine the impact of epidermal growth factor (EGF) levels on the occurrence of mucositis in cancer patients who are undergoing radiotherapy. The treatment was administered using the VMAT technique. To the best of our knowledge, this research is the first to assess EGF as it relate to radiotherapy-induced mucositis in Iraqi patients with head and neck cancer. We present this article in accordance with the STARD reporting checklist (available at https://tro.amegroups.com/article/view/10.21037/tro-23-19/rc).

AIM

The present study aims to investigate the correlation between the concentration of salivary epidermal growth factor and the development of radiation-induced mucositis in patients diagnosed with head and neck cancer.

MATERIALS AND METHODS

A cross-sectional study was conducted to assess patients undergoing external beam radiotherapy for head and neck tumours. The data was collected between October 2022 and June 2023 in Al-Andalus oncology hospital-Baghdad, utilizing a simple random sampling technique. Fifty-four patients with head and neck cancers were included in the study; diagnosis is confirmed by histopathology in every patient, with certain exclusions made. Patients, who had undergone palliative neck radiotherapy, had neck lymphoma, were in the pediatrics group, or were on-off patients that could potentially affect the interpretation of radiotherapy schedules

were excluded from the study and chosen irrespective of their age, gender, and the particular sub-site of the ailment. All patients should achieve optimal oral health before starting radiotherapy. This involves eliminating dental cavities, addressing gum and periodontal diseases, and managing any existing oral infections. In the study, all patients who participated showed no signs of distant metastasis. They underwent treatment with either a radical or adjuvant approach, receiving a dose of 2 Gy per session, administered five times a week, resulting in a total average dose of 60 Gy. External beam radiation therapy (EBRT) was administered as the sole treatment, without simultaneous chemotherapy. The radiation was delivered using the Volumetric Modulated Arc Therapy (VMAT) technique. Concurrently, patients were given systemic antifungal medication (fluconazole 100mg/day) alongside their radiotherapy. Institutional informed consent was appropriately obtained. Whole resting saliva was obtained through expectoration into graduated centrifuge tubes during 3-minute intervals from a total of fifty-four participants who were divided into three groups for the study:

- The control group consisted of patients had not undergone any radiotherapy.
- Group A included patients had received 10 sessions (20 Gy) of radiotherapy.
- Group B included patients had received 20 sessions (40Gy) of radiotherapy.

The assessment of mucositis was conducted using the World Health Organization (WHO) scoring systems [20]. The oral cavity undergoes a visual and noninvasive assessment, wherein categorization is based on the following parameters:

- Grade 0 signifies the absence of any changes.
- Grade 1 indicates the presence of pain or erythema.
- Grade 2 denotes the presence of both erythema and ulcers.
- Grade 3 signifies the presence of ulcers necessitating a liquid diet only.
- Grade 4 indicates an inability to ingest food.

The measurement of salivary EGF was conducted through the utilization of an enzyme-linked immunosorbent assay (ELISA) technique, employing a commercially available kit from USCN. The experimental procedure was carried out in accordance with the instructions provided by the manufacturer. The kit employs a sandwich enzyme-linked immunosorbent assay (ELISA) technique that specifically identifies human epidermal growth factor (EGF) and exhibits no observable cross-reactivity. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the research ethics committee of the College of Dentistry, University of Baghdad (NO. 699722). Individual consent for this retrospective analysis was waived.

ETHICAL STATEMENT

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the research ethics committee of the College of Dentistry, University of Baghdad (NO. 699722) and individual consent for this retrospective analysis was waived.

RESULTS

This research encompassed a group of 54 individuals diagnosed with head and neck cancer who were subjected to radiotherapy treatment. The participants were divided into three distinct groups. Group A consisted of 16 individuals underwent a course of 10 radiotherapy sessions. Group B comprised 21 subjects who received a total of 20 radiotherapy sessions. In contrast, Group C, serving as the control group, encompassed 17 patients did not undergo any form of radiotherapy treatment.

DEMOGRAPHIC CHARACTERISTICS

The age range of study patients was 18 to 80 years. The mean age was 47.13 ± 23.27 years in group A, 49.43 ± 20.35 years in group B, and 51 ± 21.65 years in group C. The highest proportion of study patients were > 55 years, 7(43.8%) in the group A, 10 (47.6%) in the group B, and 9(52.9%) in the control group, figure.

GENDER

Regarding gender, the proportion of males was higher than females in the group A and B (62.5% vs. 37.5%, and 57.1% vs. 42.9%), respectively, while the proportion of females was higher than males in the control group (52.9% vs. 47.1%). There was no statistically significant difference ($P \geq 0.05$) between the three groups in terms of age and gender.

Table 1. Post hoc analysis (LSD) to confirm the differences in the mean EGF expression between study groups

Biomarker	Study Groups			P – Value*
	Group A Mean ± SD	Group B Mean ± SD	Control Group Mean ± SD	
EGF	430.6 ± 220.9	489.9 ± 275.5	-	0.403
	430.6 ± 220.9	-	111.6 ± 50.73	0.001
	-	489.9 ± 275.5	111.6 ± 50.73	0.001

* Significant difference among three independent means using Post hoc analysis at 0.05 levels

Table 2. Comparison of EGF expressions according to age and gender of the studied groups

Study Groups	Age (Years)	EGF mean ± SD	P-value
Group A	< 40	461.1 ± 138.9	0.193
	40 - 55	341.6 ± 117.6	
	> 55	356.9 ± 150.7	
Group B	< 40	467.2 ± 241.1	0.386
	40 - 55	521.5 ± 221.6	
	> 55	422.2 ± 269.8	
Controls	< 40	133.8 ± 37.69	0.493
	40 - 55	91.41 ± 39.84	
	> 55	106.1 ± 59.54	
Group A	Male	446.2 ± 248.9	0.729
	Female	404.5 ± 183.1	
Group B	Male	553.7 ± 238.1	0.229
	Female	404.7 ± 112.4	
Controls	Male	113.7 ± 50.70	0.884
	Female	109.9 ± 53.76	

COMPARISON OF EGF BETWEEN STUDY GROUPS

The comparison of the mean EGF expressions between the studied groups revealed a statistically significant difference (P= 0.001) in the mean EGF expression between the three groups. Post hoc analysis (LSD) was run to confirm the differences in the mean EGF between the study groups and showed that mean EGF expressions were significantly higher in group A and group B compared with the control group (430.6 and 489.9 vs. 111.6, P= 0.001). No significant difference was found in the mean EGF between group A and group B (430.6 vs. 489.9, P= 0.403) (Table 1).

COMPARISON OF EGF ACCORDING TO AGE AND GENDER OF STUDY GROUPS

It was clear that there were no significant differences (P ≥ 0.05) in the mean EGF expressions according to the age and gender of three groups (Table 2).

COMPARISON OF EGF ACCORDING TO ORAL MUCOSITIS

In-group A, 9 patients (56.2%) developed oral mucositis, of them 4 patients were with grade1, 2 patients with grade2, and 3 patients with grade3. In the group B, 8 patients (37.1%) developed oral mucositis, of them 4 patients were with grade 1, 2 patients with grade 2, and the remaining 2 patients were with grade3. 52.9% of patient developed mucositis were male, fig 1.

The comparison of the mean EGF level in relation to the oral mucositis status of group A revealed that there were no statistically significant differences (P ≥ 0.05) in EGF expression based on the presence or absence of oral mucositis. On the other hand, within group B, the mean expression of EGF was notably lower in the patients who experienced oral mucositis compared to those who did not (326.3 vs. 590, P= 0.029) (Table 3).

CUT-OFF VALUE OF EGF EXPRESSION

Receiver operating characteristic (ROC) curve analysis was constructed for EGF level as predictor for oral mucositis. The optimal cut-off EGF for prediction of oral mucositis after radiotherapy was 502.1. Hence, EGF level < 502.1 is a predictor for oral mucositis, as a large significant area under the curve (AUC = 79.6%) indicating a significant association between the low-

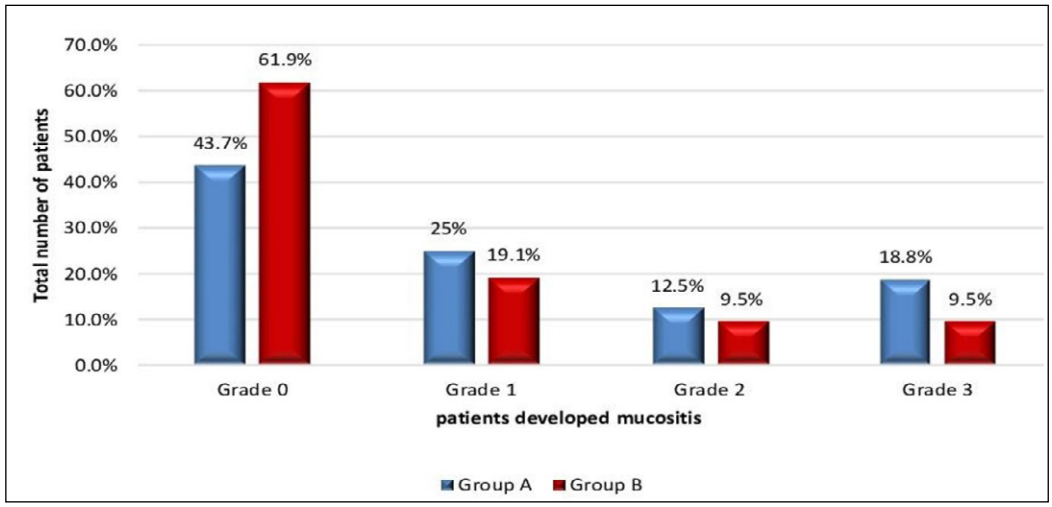

Fig. 1. Distribution of the group A and group B fig according to grading of oral mucositis

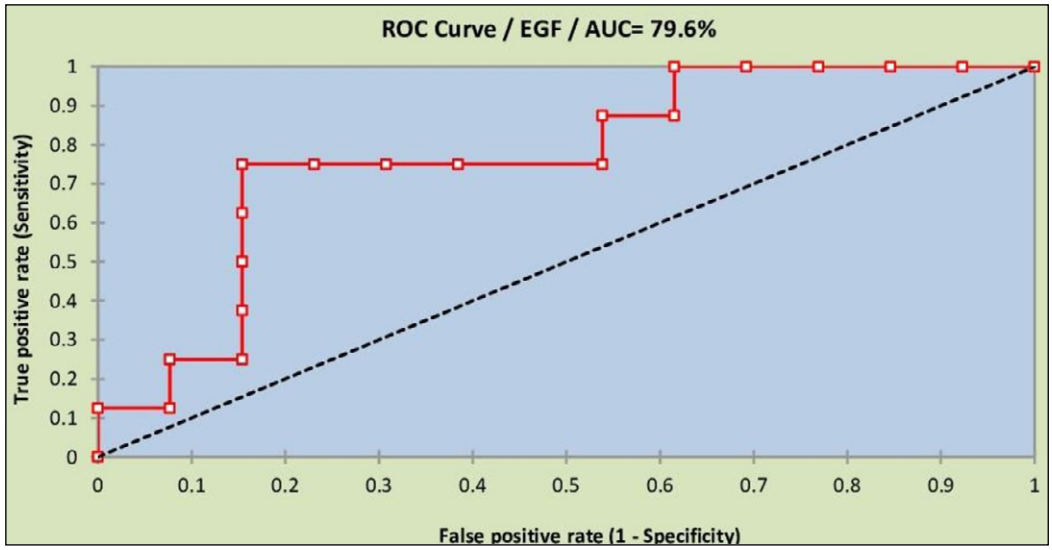

Fig. 2. ROC curve of EGF in predicting oral mucositis

er level of EGF and oral mucositis. This cut-off value obtained a sensitivity of 75% and specificity of 84.6%, with accuracy of 81%. Positive predictive value and negative predictive value of EGF were 76% and 83.6% respectively, fig. 2.

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. The categorical data is displayed using frequencies and percentages. The data exhibited a normal distribution. The statistical significance of the difference between two independent means in quantitative data was assessed using a Student t-test. The statistical significance of variations in distinct percentages (qualitative data) was assessed using the Pearson Chi-square test (χ^2-test), with the implementation of Yate's correction or Fisher Exact test when appropriate. The ability of EGF level for prediction of oral mucositis was evaluated using Receiver operating characteristic (ROC). The optimal cutoff values were determined using the Youden index.

DISCUSSION

Mucositis-related pain may be so severe that only opiate analgesics can relieve it, preventing the person from communicating or ingesting. Difficulties in swallowing can lead to dehydration, weight loss, and the requirement for nutritional assistance [21]. A reduction of function impairment, manifestation of symptoms, and financial burden related to mucositis can be achieved by carrying out of appropriate preventive and therapeutic interventions. Multiple research studies have provided evidence of an occurrence rate of oral mucositis ranging from 50% to 80% during conventional radiation therapy treatment. These findings align with the results observed in the overall population of our current study [22-23]. The occurrence of OM was found to be higher in the male population. Prior research has also identified a greater prevalence of OM in males, with reported rates of approximately 60% [24]. Furthermore, the present study observed that males exhibited a higher incidence of mucositis compared to females. The elevated prevalence among males can be elucidated by the increased

Table 3. Comparison of EGF according to oral mucositis

EGF	Oral Mucositis Mean ± SD	No Oral Mucositis Mean ± SD	t-test	P- Value*
Group A	352.6 ± 227.3	530.8 ± 179.5	- 1.699	0.111
Group B	326.3 ± 254.8	590.5 ± 244.6	- 2.366	0.029

* Significant difference of two means using independent-samples t-test at 0.05 levels

incidence of deleterious behaviors associated with this gender, including suboptimal hygiene practices, tobacco consumption, excessive alcohol intake, and infrequent utilization of dental care services [25].

In this study, oral mucositis was observed in 56.2% of patients who underwent radiation therapy for malignant disease affecting the head and neck region. These finding conflicts with a study conducted in 2016 within Baghdad oncology center, which reported an incidence of oral mucositis in 80% [26]. In the previously mentioned center in Baghdad, another study conducted in 2017 revealed that a total of 72% of patients experienced an incidence of oral mucositis [27].

These studies corroborate the findings of a previously conducted systematic review, which indicated that the incidence of mucositis is approximately 81% [28]. On the other hand, a study conducted in Brazil between January 2008 and December 2017 examined a cohort of 413 patients with head and neck cancer who underwent radiotherapy. The findings revealed that the prevalence of oral mucositis (OM) in the entire sample was 41.9%, with a higher occurrence observed among male patients (78.2%) [29]. The potential discrepancy of these studies may be attributed to a notable degree of heterogeneity observed in the treatments administered to patients across various articles, and even within individual articles, the use of different radiotherapy techniques. Noori et al. and Al-Qalamji et al. employed the 3D conformal forward planned IMRT technique, whereas this study employed the VMAT technique [26-28].

A comprehensive review of the scholarly literature was undertaken to compare the administration of doses through Volumetric Modulated Arc Therapy (VMAT) and Intensity-Modulated Radiation Therapy (IMRT) to patients with head and neck cancer. The findings indicate that the use of VMAT in the treatment of head and neck cancer leads to a decrease in adverse effects on organs at risk. This is especially significant when considering the potential impact on organs that may result in xerostomia, dysphagia, or other side effects that can significantly affect the quality of life for patients [30]. The reduction in the development of mucositis in this study may be attributed to the documented positive impact of administering antifungal medication on the severity of oral mucositis and the pain it is associated with [24].

Notwithstanding the extensively documented elevated incidence of Candida colonization in individuals with head and neck cancer who undergo radiation therapy, as reported in investigations [31-32], the current findings are weakened by the absence of evaluation of fungal status both prior to and following administration of antifungal medication, which can be attributed to practical constraints in daily clinical practice. Epidermal growth factor stands as a highly assessed biomarker in the context of oral mucositis. It is noticed a decline in EGF levels following radiation therapy and a tendency towards lower EGF levels in patients with more severe oral mucositis. These data indicate that patients who have lower levels of EGF before undergoing therapy may have a higher likelihood of experiencing mucosal injury after radiation therapy [33].

Furthermore, experimental studies have shown that the administration of EGF can potentially reduce both the severity and occurrence of oral mucositis [34]. The current study demonstrated that the average expressions of EGF were significantly elevated in both group A and group B when compared to the control group. The concentration of epidermal EGF in saliva at rest exhibited a significant increase within the initial two-week period following irradiation, No significant alterations were observed after four weeks of radiotherapy. This finding goes against a study done in 2000 that examined 18 patients with head and neck cancer.

The study revealed a decrease in the level of epidermal growth factor (EGF) in saliva after a two-week period of radiotherapy [35], which corroborates the findings of a previous study involving a cohort of 16 patients that yielded consistent results [16]. A more recent study assessed the expression of EGF in saliva before and after treatment, revealing a significant increase in EGF levels following radiation exposure [36]. Another study has suggested a potential correlation between salivary EGF levels and the extent of oral mucositis resulting from radiation therapy [33].

Nevertheless, alternative research has yielded inconclusive results, as no substantial disparity in serum or salivary levels of EGF has been observed between individuals suffering from oral mucositis and those who are deemed healthy controls [37]. This study has determined that there is an elevation in EGF levels during radiotherapy; however, it is noteworthy that the

average expression of EGF was significantly reduced in patients who developed oral mucositis, in comparison to those who did not experience this condition. In brief, this study suggests that individuals diagnosed with mucositis are those whose salivary EGF levels persist at a low level subsequent to radiation exposure. To the best of our current knowledge, this study represents the initial attempt to elucidate the cut-off value of EGF in patients with mucositis. The most favorable threshold of EGF for the anticipation of oral mucositis subsequent to radiotherapy was determined to be 502.1(pg/mL).

Therefore, a level of EGF below 502.1(pg/mL) could be predictive of oral mucositis, as evidenced by a substantial and statistically significant area under the curve (AUC = 79.6%). This suggests an interesting correlation between lower EGF levels and the occurrence of oral mucositis. The concentration of EGF in stimulated whole saliva of healthy individuals (2221.53 ± 575.92 pg/ml) was significantly higher than that in resting whole saliva (1832.60 ± 475.86 pg/ml, $P < 0.001$). This suggests that saliva stimulation, which may occur during chewing or other oral activities, plays a role in increasing EGF levels, potentially due to enhanced glandular secretion or other regulatory mechanisms. Furthermore, EGF levels in stimulated saliva were markedly elevated compared to those in serum (262.28 ± 78.06 pg/ml, $P < 0.001$) [38].

This substantial difference between saliva and serum underscores the localized secretion and action of EGF in the oral cavity, where it is likely involved in tissue repair, mucosal protection, and maintaining homeostasis. These findings are consistent with the understanding that saliva serves as a reservoir for biologically active molecules, reflecting both systemic and local physiological processes [38].

It may be difficult to establish a definitive temporal correlation between low levels of EGF and the initiation of mucositis. It is essential to determine if diminished levels of EGF occur before to the onset of mucositis or are a result of it. The study was carried out with a small sample size or with a lack of variety in terms of patient demographics (age, gender, ethnicity), thus limiting the generalizability of the results to the broader population. The concentration of epidermal growth factor (EGF) in individuals with oral mucositis can exhibit variability based on several factors.

These factors include the specific type and intensity of cancer treatment, which have undergone significant changes over the past two decades. Additionally, the stage and severity of oral mucositis, as well as the methodology employed for measuring EGF, can also contribute to the observed variations. Longitudinal studies are necessary to determine the reliability of EGF levels as a predictor over an extended period and across various phases of radiation. Furthermore, it is imperative to establish a correlation between levels of EGF and clinical outcomes that extend beyond the development of mucositis, including the duration of recovery and the responsiveness to treatment. The results obtained suggest the need for further research involving a larger group and a larger number of analyzed factors.

CONCLUSIONS

The results of the present study indicate that human epidermal growth factor (EGF) could potentially influence the healing process of radiation-induced mucosal damage. Moreover, it was observed that higher concentrations of EGF were linked to a reduced severity of mucositis in patients undergoing radiotherapy with standard daily fractions. Additionally, it is worth noting that there has been a significant decrease in the incidence of oral mucositis when comparing with previous studies that utilized outdated methods for radiation delivery.

REFERENCES

1. Al-Zahawi SM, Al-Barzenji HA. Effectiveness of prophylactic agents in prevention of oral mucositis in patients with head and neck cancer receiving radiotherapy. Therapy. 2013;3:4.
2. Pulito C, Cristaudo A, Porta CL et al. Oral mucositis: the hidden side of cancer therapy. J Exp Clin Cancer Res. 2020;39(1):210. doi: 10.1186/s13046-020-01715-7. DOI
3. Suzuki A. Chapter 10 – Management of cancer treatment-induced oral mucositis. In: Tomita H, editor. Inflammation and Oral Cancer: Academic Press. 2022, pp.183-97.
4. Hadi BAA. Effects of Low level laser therapy (LLLT) on experimentally induced oral mucositis clinical & immunohistochemistry study: College of Dentistry Effects of Low level laser therapy (LLLT). PhD thesis. 2017
5. Gormley M, Creaney G, Schache A et al. Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors. Br Dent J. 2022;233(9):780-6. doi: 10.1038/s41415-022-5166-x. DOI
6. Lechner M, Liu J, Masterson L et al. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. Nat Rev Clin Oncol. 2022;19(5):306-27. doi: 10.1038/s41571-022-00603-7. DOI

7. Ghufran Adil Hasan. Oral Mucositis in Children Suffering from Acute Lymphoblastic Leukaemia. Iraqi Dental Journal. 2014;36(1):30-3.
8. Sonis ST. New thoughts on the initiation of mucositis. Oral Dis. 2010;16(7):597-600. doi: 10.1111/j.1601-0825.2010.01681.x. DOI
9. Forné ÁF, Anaya MJG, Guillot SJS et al. Influence of the microbiome on radiotherapy-induced oral mucositis and its management: A comprehensive review. Oral Oncology. 2023;144:106488. doi: 10.1016/j.oraloncology.2023.106488. DOI
10. Boonstra J, Rijken P, Humbel B et al. The epidermal growth factor. Cell Biol Int. 1995;19(5):413-30. doi: 10.1006/cbir.1995.1086. DOI
11. Waterfield M. Epidermal growth factor and related molecules. The Lancet. 1989;333(8649):1243-6. doi: 10.1016/s0140-6736(89)92339-8. DOI
12. Ohshima M, Sato M, Ishikawa M et al. Physiologic levels of epidermal growth factor in saliva stimulate cell migration of an oral epithelial cell line, HO – 1 – N – 1. Eur J Oral Sci. 2002;110(2):130-6. doi: 10.1034/j.1600-0722.2002.11179.x. DOI
13. Agha-Hosseini F, Mohebbian M, Sarookani M-R et al. Comparative evaluation of EGF in oral lichen planus and oral squamous cell carcinoma. Acta Med Iran. 2015;53(8):471-5.
14. Schoichet JJ, Mourão C, Fonseca EM et al. Epidermal Growth Factor Is Associated with Loss of Mucosae Sealing and Peri-Implant Mucositis: A Pilot Study. Healthcare (Basel). 2021;9(10):1277. doi: 10.3390/healthcare9101277. DOI
15. Chen W, Yang C, Xue H et al. The protective effect and mechanism of epidermal growth factor on necrotizing enterocolitis in a neonatal rat model. Transl Pediatr. 2021;10(4):900-13. doi: 10.21037/tp-21-81. DOI
16. Epstein JB, Emerton S, Guglietta A et al. Assessment of epidermal growth factor in oral secretions of patients receiving radiation therapy for cancer. Oral Oncol. 1997;33(5):359-63. doi: 10.1016/s1368-8375(97)00009-2. DOI
17. Dumbrigue HB, Sandow PL, Nguyen K-HT et al. Salivary epidermal growth factor levels decrease in patients receiving radiation therapy to the head and neck. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;89(6):710-6. doi: 10.1067/moe.2000.106343. DOI
18. Schapher M, Wendler O, Gröschl M. Salivary cytokines in cell proliferation and cancer. Clinica Chimica Acta. 2011;412(19):1740-8. doi: 10.1016/j.cca.2011.06.026. DOI
19. Al-Taie A, Al-Shohani AD, Albasry Z et al. Current topical trends and novel therapeutic approaches and delivery systems for oral mucositis management. J Pharm Bioallied Sci. 2020;12(2):94-101. doi: 10.4103/jpbs.JPBS_198_19. DOI
20. WHO G. Handbook for reporting results of cancer treatment. WHO offset publication. 1979;48:1-41.
21. Murphy BA. Clinical and economic consequences of mucositis induced by chemotherapy and/or radiation therapy. J Support Oncol. 2007;5(9):13-21.
22. Elting LS, Cooksley CD, Chambers MS et al. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys. 2007;68(4):1110-20. doi: 10.1016/j.ijrobp.2007.01.053. DOI
23. Sonis ST. Mucositis: The impact, biology and therapeutic opportunities of oral mucositis. Oral Oncol. 2009;45(12):1015-20. doi: 10.1016/j.oraloncology.2009.08.006. DOI
24. Nicolatou-Galitis O, Kouloulias V, Sotiropoulou-Lountou A et al. Oral mucositis, pain and xerostomia in 135 head and neck cancer patients receiving radiotherapy with or without chemotherapy. The Open Cancer Journal. 2011;4(1). doi: 10.2174/1874079001104010007. DOI
25. Wuketich S, Hienz SA, Marosi C. Prevalence of clinically relevant oral mucositis in outpatients receiving myelosuppressive chemotherapy for solid tumors. Support Care Cancer. 2012;20(1):175-83. doi: 10.1007/s00520-011-1107-y. DOI
26. Noori AGM, Al-Rawaq KJ, Al-Nuaimi DSA et al. Quality of life during head and neck external beam radiotherapy. Med Sci. 2019;23(95):125-9.
27. Al-Qalamji MAN, Al-Rawaq KJ, Al-Nuaimi DSA et al. Oral mucositis in patients undergoing radiotherapy for head and neck cancer: An observational cross-sectional study. F1000Research. 2019;8:179.
28. Pacheco R, Cavacas MA, Mascarenhas P et al., editors. Incidence of Oral Mucositis in Patients Undergoing Head and Neck Cancer Treatment: Systematic Review and Meta-Analysis. Med. Sci. Forum. 2021;5(1):23. doi: 10.3390/msf2021005023.
29. Pereira IF, Firmino RT, Meira HC et al. Radiation-induced oral mucositis in Brazilian patients: prevalence and associated factors. In Vivo. 2019;33(2):605–609. doi: 10.21873/invivo.11517. DOI
30. Buciuman N, Marcu LG. Dosimetric justification for the use of volumetric modulated arc therapy in head and neck cancer—A systematic review of the literature. Laryngoscope Investig Otolaryngol. 2021;6(5):999–1007. doi: 10.1002/lio2.642. DOI
31. Debta P, Swain SK, Sahu MC et al. Evaluation of Candidiasis in Upper-Aerodigestive Squamous Cell Carcinoma Patients-A Clinico-Mycological Aspect. Int J Environ Res Public Health. 2022;19(14). doi: 10.3390/ijerph19148510. DOI
32. Chitapanarux I, Wongsrita S, Sripan P et al. An underestimated pitfall of oral candidiasis in head and neck cancer patients undergoing radiotherapy: an observation study. BMC Oral Health. 2021;21(1):353. doi: 10.1186/s12903-021-01721-x. DOI
33. Normando AGC, Rocha CL, de Toledo IP et al. Biomarkers in the assessment of oral mucositis in head and neck cancer patients: a systematic review and meta-analysis. Supportive Care in Cancer. 2017;25:2969-88. doi: 10.1007/s00520-017-3783-8. DOI
34. Santa Maria PL, Capasso R, Beswick D. Method for Treating or Preventing Radiotherapy-and Chemotherapy-Associated Oral Mucositis Using Locally Administered Heparin Binding Epidermal Growth Factor Like Growth Factor (HB-EGF). Sci Rep. 2020;10:17327. doi: 10.1038/s41598-020-73875-7. DOI

35. Epstein JB, Gorsky M, Guglietta A et al. The correlation between epidermal growth factor levels in saliva and the severity of oral mucositis during oropharyngeal radiation therapy. Cancer. 2000;89(11):2258-65. doi: 10.1002/1097-0142(20001201)89:11<2258::aid-cncr14>3.0.co;2-z. DOI
36. Russo N, Bellile E, Murdoch-Kinch CA et al. Cytokines in saliva increase in head and neck cancer patients after treatment. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(4):483-90.e1. doi: 10.1016/j.oooo.2016.05.020. DOI
37. Logan RM, Al-Azri AR, Bossi P et al. Systematic review of growth factors and cytokines for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer. 2020;28:2485-98. doi: 10.1007/s00520-019-05170-9. DOI
38. Ding Y, Su JZ, Yu GY. Comparison of epidermal growth factor expression and secretion in human salivary glands. Arch Oral Biol. 2024;164:105989. doi:10.1016/j.archoralbio.2024.105989. DOI

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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