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The Effect of Two Different Techniques of Head and Neck Radiotherapy on Saliva Secretion and Salivary Immunoglobulin A

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ABSTRACT

Background: Head and neck cancer (HNC) mean a heterogeneous group of tumors in multiple anatomical sites in the head and neck structures. Radiation therapy(RT) is one of the fundamental treatment options for tumors. Saliva is a clear, mucoserous fluid produced in the mouth which determines the environment of the oral structures. Immunoglobulin A (IgA) can considered to be the major specific protection mechanism in the mouth.

Aims of study: To monitor the effects of two techniques of head and neck radiotherapy on salivary flow rate (SFR) and salivary IgA.

Materials and method: The study included thirty healthy individuals as control group and two patients groups with HNC: the first group consist of 30 patients treated by three dimensional conformal radiation therapy (3DCRT) and the second group also consist of the same patient's number but treated by intensity-modulated radiation therapy (IMRT)) at middle Euphrates oncology center/ Najaf-Iraq. Saliva samples were collected before the first session and after the last session of RT.

Results: The study shows highly significant decrease in SFR in both patients groups after finishing RT. The SFR in patients treated by IMRT is significantly higher than SFR in other group treated by 3DCRT. Salivary IgA is significantly reduced after RT, without difference statically in the level of IgA between the two patients group.

Conclusion: The present study shows that head and neck RT decrease both SFR and salivary IgA, at the same time IMRT technique is better than 3DCRT in maintaining saliva secretion.

Key words: Head and neck cancer; radiation therapy; salivary flow rate; salivary IgA.

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INTRODUCTION

Head and neck cancer (HNC) mean a heterogeneous group of tumors in multiple anatomical sites in the head and neck structures [(1)] such as oral and sinonasal cavity, pharynx, larynx and salivary glands. [(2, 3)]

The majority (nearly 95%) of HNC cases are squamous cell carcinomas (HNSCC) that is from epithelial origin [(3)], also Rischin et al [(4)] mentioned that represent more than 90% of HNC cases.

Saliva is a clear, mucoserous fluid produced in the mouth by three pairs of major and about 450-800 minor salivary glands. The term whole saliva is mean the mixture consist of saliva, mucosal surface transudations, gingival crevicular fluid, desquamated epithelium, expectorated respiratory secretions, bacteria, viruses and fungi. [(5)] Whole saliva determines the environment of the oral structures. [(6)]

Immunoglobulin A (IgA) is an antibody that plays a definitive role in immunity of mucosal surfaces Immunoglobulin A is accounting about 70% of total antibodies in the body; although its serum concentration considered low, IgA is concentrated in mucosal secretions such as saliva, milk, tears, nasal, intestinal and respiratory secretions. [(7)]

Salivary IgA is the notable antibody and can considered to be the major specific protection mechanism in the mouth [(8)] , as it serves many functions including preventing adherence of microbes to the mucosal surfaces, neutralizing viruses and toxins as well as do synergizing action with other immunological factors like lactoferrin and lysozymes. [(9)]

Radiotherapy (RT), also known as radiation therapy, is a treatment option based on the use of high energy rays or radioactive materials, to damage cancerous cells and to stop cellular growth and division. [(10)]

Radiation therapy is one of the fundamental treatment options for tumors. It is widely used as cancer treatment strategy, with about 60% of patients with solid malignancy will receive curative or palliative radiation as part of their therapy. [(11)]

The dysfunction of salivary glands is a significant and usually permanent adverse effect of the head § neck radiation therapy that has considerable knock on effects, negatively impact the life quality. [(12)]

Most of patients receiving radiation therapy to head and neck region developed hypo salivation with noticeable change in volume, consistency as well as pH of saliva.[(13)]

The three dimensional conformal radiation therapy (3DCRT) based on computed tomography imaging which facilitates accurate localization of the tumor and critical surroundings normal structures for best external beam placement. [(14)]

The planning of the radiation can be conformed to the tumor shape and size thus minimizing the radiation dose up to 50% to normal organs and tissues and this in turn decrease late hazards [(15)], but the normal tissues still receive a high dose of radiation because radiotherapy is delivered in approximately three fields with a same dose in every field. [(16)]

Intensity-modulated radiation therapy(IMRT) is an enhanced model of high-precision RT that used computer controlled linear accelerator to deliver precise radiation doses

to the tumor or to specific areas inside the tumor tissue and now it's widely used to treat HNC. [17]

The advantage of IMRT is sparing the important vital organs and tissues such as parotid and submandibular salivary glands, mucosal tissue of digestive tract and hypo pharyngeal muscles. [15]

MATERIALS AND METHODS

The study included two patients groups with HNSCC: the first group consist of 30 patients treated by 3DCRT: and the second group also consist of the same patient's number but treated by IMRT.

The total 60 patients were 34 males and 26 females, aged between 19-81 years with mean± standard deviation(SD) was (56.3±14.5) years, diagnosed with HNSCC and treated by their oncologist as shown in(figure 1) at middle Euphrates oncology center/ Najaf-Iraq for the period between April 2018 to June 2019 as shown in table 1.

The treatment period for was continued for all patients between five to seven weeks scheduled as five days every week and the daily fraction was (1.8 - 2.2) gray. The mean dose of whole radiation for the first group treated by 3DCRT was (66.1±5.2) gray, and the radiation dosage was (64.9±5.3) gray for the second patients group treated by IMRT.

The control group was 30 persons (17 males and 13 females), they were looking healthy without any signs or symptoms of systemic diseases, as can as possible match the patients groups in gender and age, with mean ±SD of age was (54.3±14.4) years.

Table 1: Display age, gender and tumor site of patients.

Variable		Value		
Patients groups		First group of patients *	Second group of patients **	Total
Gender	Male	18	16	34
	Female	12	14	26
Age in years	Mean± Standard deviation	54.8± 16.2	57.7± 12.8	56.3± 14.5
Tumor location	Oral cavity	9	7	16
	Oropharynx	6	4	10
	Nasopharynx	5	9	14
	Larynx	4	3	7
	Hypopharynx	3	1	4
	Nasal cavity	1	3	4
	Paranasal sinuses	2	3	5

*= Patients treated by 3DCRT, **= Patients treated by IMRT

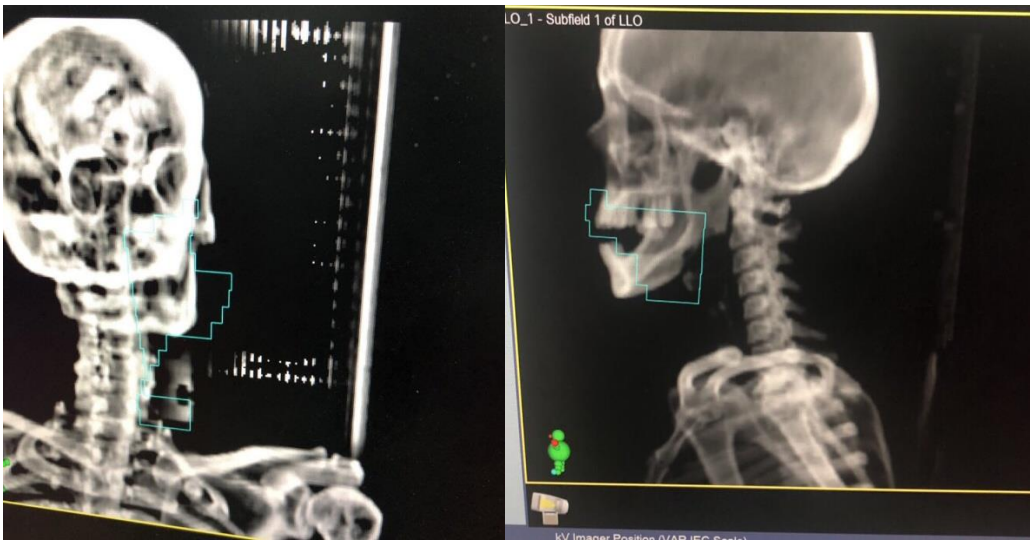

Figure (1): Two different patients with HNSCC receiving radiotherapy.

All patients were informed about the purpose and goal of this study, hazards and benefits and timing of procedures and after their acceptance in participation, they asked to sign in informed consent.

2.1 Saliva collection

The patients instructed to tilt their heads forward and spit into graduated plastic jar for 10 minutes. The unstimulated saliva was collected from patients at two timing, the first was a half hour before the first session of radiotherapy and the second timing was half hour after the last session of RT, all samples was collected at morning to minimize daily variation, also the patients instructed to don't eat, drink or use any gum one hour before sample collection. [18, 19, 20] The saliva samples were stored temporarily in ice box, then centrifuged at 4000 round per minute for ten minutes, after that the supernatant was aspirated and stored at -30 C until the time of analysis by enzyme-linked immunosorbent assay (ELISA).

RESULTS

The table (2) and present salivary flow rates (mean ±SD) for control subjects (1.6±0.29) and patients pre-radiotherapy (1.67±0.22) with no difference statically between them (P-value=0.28).

There is highly significant decrease in mean of salivary flow rate between two recordings of same group of patients before radiotherapy (1.68±0.25) and post (3D) technique (0.49±0.18) with (P-value<0.001). Also there is highly significant decrease (p-value< 0.001) in salivary flow rate of patients' pre-treatment (1.66±0.2) and post-IMRT (0.94±0.27).

In comparison between the two treatment arms, the flow rate of patients after finishing IMRT (0.94±0.27) is higher significantly than the flow rate of patients after 3DCRT (0.49±0.18) with (P-value<0.001).

The study presents salivary IgA level (mean ±SD) in ng/ml for control subjects (644.7±205.4), and total patients pre-radiotherapy (747.6±244.6), with significant increase (P-value=0.04) in patients group when compared to control.

There is a significant decrease in mean of salivary IgA level between two readings of the same group of patients before starting treatment (728.7±247.8) and after 3DCRT (553.5±252.1) with (P-value=0.009). Also there is statically significant decrease (p-value= 0.002) in salivary IgA level of patients pre-treatment (766.6±244) and post-IMRT (562.2±240.8) as shown in table (3).

The study doesn't show any static difference in the salivary IgA level between patients finishing IMRT and patients finishing (3D) technique with (P-value=0.89).

Table 2: presents the mean of salivary flow rate with p-value in different groups. HS=highly significant, NS=Non-significant.

Subject	Groups	N	Mean ± SD	Range	P-value
Salivary flow rate (ml/5minutes)	Control	30	1.6±0.29	0.8-2.1	0.28 NS
	Total patients pre-radiotherapy	60	1.67±0.22	1-2.1	
	Patients pre-3DCRT	30	1.68±0.25	1-2.1	< 0.001 HS
	Patients post-3DCRT	30	0.49±0.18	0.2-1	
	Patients pre-IMRT	30	1.66±0.2	1.3-2	< 0.001 HS
	Patients post-IMRT	30	0.94±0.27	0.4-1.5	
	Patients post-3DCRT	30	0.49±0.18	0.2-1	< 0.001 HS
	Patients post-IMRT	30	0.94±0.27	0.4-1.5	

Table 3: presents the mean ± SD of salivary IgA with p-value in patient pre and post radiotherapy.

Marker	Groups	Number	Mean ± SD	Range	P-value
Salivary IgA (ng/ml)	Control	30	644.7± 205.4	294-1030	0.04
	Total patients pre-radiotherapy	60	747.6± 244.6	169.7 1271	
	Patients pre-3DCRT	30	728.7±247.8	169.7 1217	0.009
	Patients post 3DCRT	30	553.5±252.1	142.9-984	
	Patients pre-IMRT	30	766.6±244	174-1171	0.002
	Patients post-IMRT	30	562.2±240.8	287-1032	
	Patients post 3DCRT	30	553.5±252.1	142.9-984	0.89
	Patients post-IMRT	30	562.2±240.8	287-1032	

DISCUSSION

The flow rate show no difference statically between control and HNC patients pre-treatment, this is in agreement with several studies by Sreebny et al., [21] , Greer et al., [22] , Spolidorioe et al., [23] and Pontes et al., [24] , when they found the (p-value>0.05) between patients group before radiotherapy and control group. The explanation of this study and previous study by Pontes et al., [24] this decrease of the salivary rate is straight forwardly connected to radiotherapy treatment and not to the presence of malignant growth. That's mean, a patient with head and neck malignancy preceding radiotherapy, has an ordinary salivary rate.

The same result of salivary flow rate significant decrease after radiation treatment to head and neck tumors mentioned by several studies. [13, 25, 26, 27, 28, 29, 30]

This early hypo salivation might be because harm to the signal transduction framework plasma layer of acinar cells, affecting the signaling routes of water discharge and no quick cell death happens or classical cellular death of both progenitor and stem cells interfere with the normal cell renewal, and cause changes to the cell environment therefore, secretary cells improperly work for a short period. [31, 32]

The study presents the flow rate of patients after finishing IMRT is higher significantly than the flow rate of patients after 3DCRT. This agree with Kam et al., [33] when they found significantly higher salivary flow in IMRT patients rather than other patients group treated by conventional radiation, also agree with Maria Golen et al., [34] and Fatema et al., [35] as they compare the fall in percentage of salivary excretion after IMRT and conventional radiotherapy, they found less fall in excretion percentage in IMRT rather than more fall in conventional technique. This difference is due to that in IMRT always there is sparing of important vital structures like salivary glands. [15, 36, 37, 38]

This increase in salivary IgA is matching with previous studies as Brown et al., [39] and Saman et al., [40], when they reported statically elevation of salivary IgA in HNCSCC patients when compared to control. Similar results of salivary IgA elevation in patients with oral cancer in comparison to healthy individuals. [41, 42, 43] On the other hand several studies reported a statically significant reduction of salivary IgA in patients with oral cancer when compared to control. [44, 45] They was suggested that this decrease may be due to a regional immune suppression and evidenced by increased susceptibility of patients with oral cancer to infection. [46]

The explanation of salivary IgA elevation in this study is due to increase local production of IgA in response to local tumor with associated surroundings infection and increase antigenic inflammatory stimuli. [42, 47]

The reduction of salivary IgA after radiotherapy agrees with Hussein, [48] and Wu et al., [49]. It can be explained by the radiation has an adverse effect on actions of both T and B lymphocytes and as known these cells controlled the production of immunoglobulin. [50, 51] Another explanation of this reduction is that salivary IgA is secreted by plasma cells and pass through the epithelial cells receptors into lumen. It looks alike that radiotherapy causes damage to epithelial cells and so impair the transudation of secretory IgA into saliva. [29]

The study concluded that reduction in both salivary IgA and salivary flow rate is due to radiotherapy and not due to disease its self and even IMRT for head and neck cancer affecting saliva secretion, but it's much less than its reduction after 3DCRT.

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