RESEARCH

Changes of parotid and submandibular glands caused by radiotherapy—an ultrasound evaluation

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Objective: Radiotherapy may alter the normal morphology of salivary glands located in the radiation field. These changes could be evaluated safely by sonography; however, there have been few studies in this regard. This study is aimed at evaluating the sonographic changes of the parotid and submandibular glands in patients undergoing radiotherapy for head and neck malignancies.

Methods: 20 patients (16 males and 4 females) with head and neck malignancies who had been referred for radiotherapy to the Qaem Hospital in Mashhad, Iran, entered the study. Length, height, depth, echotexture, echogenicity and margins of parotid and submandibular glands were evaluated in three stages (I, before radiotherapy; II, 2 weeks after radiotherapy; and III, 6–7 weeks after radiotherapy) using sonography. Peak systolic velocity (PSV), end diastolic velocity (EDV) and resistive index (RI) were also evaluated by Doppler sonography.

Results: Significant differences in length, height and depth ($p = 0.000$, $p = 0.000$, and $p = 0.39$, respectively) and also echotexture, echogenicity and gland margins ($p = 0.000$) were observed before and after radiotherapy. Doppler sonography results showed no significant differences regarding PSV, EDV and RI between sonographic stages. Echotexture and echogenicity were the only independent parameters that showed significant differences in sonographic stages I and II ($p = 0.000$). Length in stage I and II ($p = 0.000$) and echogenicity in stage III ($p = 0.038$) were the only parameters that showed significant differences between the two glands.

Conclusion: Radiotherapy may change the echotexture, echogenicity and margins of the salivary glands from homogenic to heterogenic, hyperechoic to hypoechoic and regular to irregular, respectively, and may reduce their size.

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Keywords: radiotherapy; sonography; salivary gland; Doppler sonography; head and neck malignancies

Introduction

Head and neck malignancies comprise 3–5% of all malignancies. Radiotherapy is a major treatment method for these malignancies. An important complication of radiotherapy for head and neck malignancies is its potential to damage the main salivary glands.¹ Main

salivary glands inevitably receive radiation during mouth cavity and nasopharynx radiotherapy for head and neck malignancies.² Mouth dryness is the most common complication in patients who received radiotherapy for their head and neck malignancies.¹ Saliva flow reduces by 50–60% during the first week of radiotherapy and after 6 weeks of radiotherapy and 60 Gy radiation it reaches 0%.^{1,3} This complication is more common among patients who receive bilateral radiotherapy.³ The radiation uptake by salivary glands

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alters the parenchymal structure and vascularity which result in volume and viscosity changes of secreted saliva.¹ Salivary gland parenchyma is very sensitive to radiation (the parotid gland is more sensitive compared with the submandibular gland).³

Bergorie was the first to describe radiotherapy-induced damage of salivary glands in 1911.² However, the mechanism of such damage is still unknown. Several changes happen in tissues located within the radiation field after radiotherapy. Various imaging techniques, including CT scan, MRI and sonography, were used to evaluate these changes.^{4,5} Sonography is a simple and safe technique for the evaluation of salivary gland changes caused by radiotherapy.⁵ Salivary glands after radiotherapy have been reported as hypoechoic and heterogenic in sonography.^{6–8} Peak systolic velocity (PSV), end diastolic velocity (EDV) and resistive index (RI) also showed below normal values in sonography.⁶

However, there have been few data reported regarding the changes in salivary glands following radiotherapy for head and neck malignancies. This study is designed and conducted to evaluate the changes in parotid and submandibular glands in patients with head and neck malignancies undergoing radiotherapy treatment using greyscale and Doppler sonography.

Material and methods

In this cross-sectional descriptive study, 20 patients (16 males and 4 females) aged 10–80 years with head and neck malignancies referred to the Radiotherapy–Oncology Department of the Qaem Hospital in Mashhad, Iran, were evaluated. Parotid and submandibular glands of the selected patients were evaluated using greyscale and Doppler sonography. Parameters including length, width, depth, echotexture, echogenicity and gland margins for greyscale sonography and PSV, EDV and RI for Doppler sonography were measured in three stages.

Inclusion criteria:

- having healthy parotid and submandibular glands in the field of radiotherapy
- parotid and submandibular glands' received radiation dosage exceeding 5000 cGy.

Exclusion criteria:

- presence of associated diseases such as Sjögren's disease, salivary gland masses, human immunodeficiency virus or autoimmune diseases
- history of previous radiotherapy or surgical procedures in the head and neck regions.

All patients received radiotherapy using cobalt 60 apparatus (Theratron®; Nordion, Kanata, Canada)

with γ -waves. Radiotherapy was performed in two lateral fields similar to the standard procedure for head and neck malignancies in radiotherapy protocol. The patients received 10 Gy radiation/week (2 Gy daily for 5 days/week) and a total of 60–66 Gy. All patients also simultaneously received chemotherapy with 40 mg m⁻² cisplatin weekly.

Of 20 evaluated patients, 14 had nasopharynx carcinomas, 3 had larynx squamous cell carcinoma and 3 had hypopharynx carcinomas.

All patients were informed about the aims of the study and procedures prior to the evaluations and written consent was received from each patient.

Sonographic evaluation was performed using a 7–12 MHz multifrequency linear transducer (Ultrasonix, Toronto, Canada). Real-time ultrasonography images were produced for the parotid and submandibular glands on both sides. To evaluate the rest blood flow, patients were asked to stay in the supine position for at least 5 min before the sonographical procedures. Sonographical evaluations were performed by an expert radiologist at Qaem Hospital in three stages: I, prior to the radiotherapy; II, 2 weeks after radiotherapy;^{9,10} and III, 6–7 weeks after radiotherapy.³ Length and width were measured for each parotid and submandibular gland while depth was measured for parotid glands only. To evaluate the length of the parotid gland, the probe was situated longitudinally behind the ramus of the mandible and the maximum value was measured. For patients whose parotid gland was bigger than the field of view, dual images were produced and complied with the gland image (Figure 1). To evaluate the length of submandibular gland, the probe was situated parallel to the inferior edge of the mandible and the maximum value was measured (Figure 2).

The widths of parotid and submandibular glands were also measured by placing the probe vertically in the middle of the ramus of the mandible and vertically to the body of the mandible, respectively, and the maximum values were measured (Figure 3). To perform a better evaluation of the parotid gland, we also

Figure 1 Measurement of the longitudinal dimension of parotid gland, by dual images, in cases where the parotid gland was larger than the field of view

Figure 2 Measurement of the longitudinal dimension of submandibular gland

measured the depth of the gland in 50% of the cases. The depth was identified as the distance between the retromandibular vein and the gland capsule (Figure 4).

Gland margins, echogenicity and echotexture were also evaluated. Echogenicity is described as hyperechoic (denoting a region in an ultrasound image in which the echoes are stronger than normal or than surrounding structures), isoechoic (a region in an ultrasound image in which the echoes are similar to the surrounding region) and hypoechoic (a region in an ultrasound image in which the echoes are weaker or fewer than normal or than in the surrounding regions) in comparison with the adjacent muscles. Echotexture was identified as homogeneous or heterogeneous. Gland margins were considered as regular or irregular. PSV, EDV and RI were also measured using Doppler sonography (Figure 5).

The data were collated and analysed using SPSS v.14 (IBM Corporation, formerly SPSS Inc., Armonk, NY). The Friedman test was employed to compare the data distribution among more than two dependent variables and the Mann–Whitney test was used to compare quantitative values between two independent groups. χ^2 and Fisher's exact tests were employed to analyse the independent values of qualitative variables. Relevant tables were also produced to discuss the results. *p*-values of <0.05 were considered significant.

Figure 3 Measurement of the transverse dimension of parotid gland

Figure 4 Measurement of the depth dimension of parotid gland

Results

20 patients were evaluated by greyscale and Doppler sonography. The total evaluated glands included 40 parotid and 40 submandibular glands owing to the bilateral sonographic evaluations and also the qualitative and quantitative differences between the glands in both sides. The mean age of the patients was 48.7 ± 15.01 years and they were aged 18–80 years.

Figure 5 Doppler sonogram of a parotid gland showing measurement of blood flow velocity (peak systolic velocity and end diastolic velocity) and vascular resistance (resistive index) of the gland

Table 1 Correlation of the longitudinal, transverse and depth dimension of parotid and submandibular glands with sonographic stages

Type of gland	Dimension	Stage	Number of patients	Minimum (mm)	Maximum (mm)	Mean $\pm$ SD (mm)	p-value
Parotid	Transverse	I	40	17	40	22.1 $\pm$ 4.03	0.000
		II	32	13	28	19.16 $\pm$ 3.77	
		III	30	8	27	15.9 $\pm$ 4.36	
	Longitudinal	I	40	28	70	51.68 $\pm$ 9.47	0.000
		II	32	23	56	43.69 $\pm$ 9.71	
		III	30	20	50	38.53 $\pm$ 7.61	
	Depth	I	14	6	13	9 $\pm$ 2.38	0.039
		II	10	5	9	7 $\pm$ 1.33	
		III	8	4	8	8 $\pm$ 1.45	
Submandibular	Transverse	I	40	11	36	22.92 $\pm$ 7.31	0.00
		II	32	9	35	21.09 $\pm$ 7.16	
		III	30	7	30	18.13 $\pm$ 7.75	
	Longitudinal	I	40	22	44	33.45 $\pm$ 5.84	0.00
		II	32	22	42	31.34 $\pm$ 5.60	
		III	30	20	38	27.47 $\pm$ 4.83	

SD, standard deviation.

Stages: I, before radiotherapy; II, 2 weeks after radiotherapy; III, 6–7 weeks after radiotherapy.

We found significant differences regarding length and width ($p = 0.000$) in both parotid and submandibular glands and depth ($p = 0.039$) in parotid glands between different sonography stages (Table 1). Length and width of both glands reduced during the treatment period.

Echotexture, echogenicity (Table 2) and gland margins showed significant differences between different sonography stages ($p = 0.000$). Echotexture, echogenicity and gland margins changed to heterogenic, hypoechoic and irregular, respectively, during the radiotherapy.

PSV, EDV and RI were measured for 36 parotid and 35 submandibular glands. No significant difference was observed regarding PSV, EDV and RI between different sonography stages (Table 3). PSV and RI values were reduced during the treatment period.

Independency of echotexture, echogenicity and gland margins were also evaluated and no significant relation was observed between these variables except for echotexture and echogenicity in stage II of sonography ($p = 0.000$).

Patients were divided into two age groups, > 49 years and ≤ 49 years, to evaluate the relationship between age and salivary gland sensitivity to radiation. All parameters except parotid gland PSV in stage II ($p = 0.023$), parotid gland EDV in stage II ($p = 0.007$), submandibular gland margin in stage II ($p = 0.003$) and submandibular gland length in stage III ($p = 0.039$) were independent. Patients below the age of 49 years showed more changes in their glands.

All qualitative and quantitative variables were compared and only length in stages I and II ($p = 0.011$) and echogenicity in stage III ($p = 0.038$) showed significant differences between parotid and submandibular glands.

Discussion

Sonography is a cheap, safe and accessible technique for the evaluation of the patients.¹¹ It is also very valuable for monitoring the changes in salivary glands caused by radiotherapy and provides important data regarding the morphologic changes of the glands.⁶ Owing to the scarcity of published data about the changes in salivary glands following radiotherapy, the present study evaluated these changes, employing sonography as the evaluation technique.

We observed several changes including the reduction of length, width and depth of parotid glands during the three stages of sonography, as well as the reduction of length and width of submandibular glands. This reduction was also statistically significant for all values. These changes were different from those occurring in other organs following radiotherapy, including inflammation, swelling and hyperthermia, which result in the increase in the size of the organ.¹² Nomayr *et al*¹³ found similar results about the changes of salivary glands using MRI for the evaluation. Radfer *et al*¹⁴ conducted a study on guinea pigs and reported similar results to our findings.

Table 2 Frequency distribution of the parotid and submandibular glands' echotexture and echogenicity in sonographic stages

Type of gland	Stage	Echotexture		Echogenicity		
		Homogenic	Heterogenic	Hyperchoic	Isoechoic	Hypoechoic
Parotid	I	40	0	36	4	0
	II	22	10	20	0	12
	III	2	28	0	0	30
Submandibular	I	40	0	36	4	0
	II	24	8	18	2	12
	III	2	28	0	4	26

 $\chi^2 = p = 0.000$. Stages: I, before radiotherapy; II, 2 weeks after radiotherapy; III, 6–7 weeks after radiotherapy.

Table 3 Correlation of the parotid and submandibular glands' peak systolic velocity (PSV), end diastolic velocity (EDV) and resistive index (RI) with sonographic stages

Type of gland	Vascular index	Stage	Number of patients	Minimum (mm s^{-1})	Maximum (mm s^{-1})	Mean $\pm$ SD (mm s^{-1})	p-value
Parotid	PSV	I	36	12	100	48.25 $\pm$ 25.40	0.135
		II	32	17	98	37.66 $\pm$ 21.01	
		III	30	8	96	36.17 $\pm$ 20.49	
	EDV	I	36	7	52	21.52 $\pm$ 11.22	0.464
		II	32	4	69	15.56 $\pm$ 12.28	
		III	30	3	70	18.93 $\pm$ 14.27	
	RI	I	36	0.480	0.930	0.662 $\pm$ 0.103	0.264
		II	32	0.560	0.850	0.660 $\pm$ 0.079	
		III	30	0.500	0.820	0.654 $\pm$ 0.092	
Submandibular	PSV	I	35	9	92	42.74 $\pm$ 25.35	0.794
		II	31	13	91	38.06 $\pm$ 21.34	
		III	30	7	75	35.57 $\pm$ 18.63	
	EDV	I	35	5	64	18.63 $\pm$ 13.11	0.291
		II	31	6	47	17.32 $\pm$ 10.98	
		III	30	9	92	22.13 $\pm$ 20.23	
	RI	I	35	0.490	0.890	0.644 $\pm$ 0.084	0.926
		II	31	0.380	0.380	0.609 $\pm$ 0.106	
		III	30	0.350	0.350	0.615 $\pm$ 0.093	

SD, standard deviation.

Stages: I, before radiotherapy; II, 2 weeks after radiotherapy; III, 6–7 weeks after radiotherapy.

Orloff *et al*, Burke *et al* and Ying *et al* also reported similar results.^{5,6,8} However, Ying *et al* only reported a significant difference regarding the width of the parotid glands.⁶ Eva *et al* suggested that the size of salivary glands only changes in acute situations, while in chronic situations the size decreases owing to the atrophy.⁷ It is also stated that the reduction in size of the gland may be a result of parenchymal damage and acinar atrophy.^{14,15}

In our study, all glands had homogenic echotexture in the first stage of sonography, which changed to heterogenic in the next stages. Ying *et al*, Orloff *et al*, Gritzmann *et al* and Eva *et al* also reported the same findings.^{6–8,16} The organized placement of acini in normal salivary glands may produce their homogenic echotexture, while acini destructions by radiotherapy associated with abnormally large acini may cause the heterogenic echotexture following radiotherapy.^{15,17} Chronic sialoadenitis with inflammation and fibrose is also reported after radiotherapy.^{14,18–20} The heterogenic echotexture may also be due to these inflammatory areas, which were observed as hypoechoic areas in sonography.⁶ The same sonographical view is reported in Sjögren's syndrome.²¹

Salivary glands were hyperechoic or isoechoic compared with adjacent muscles in the first stage of sonography, but their echogenicity changed to hypoechoic as the stages of sonography progressed. Ying *et al*, Evan *et al*, Howlett *et al* and Eva *et al* reported similar results.^{6,7,22,23} Normal acini and granules can reflect the ultrasound waves as a reflective interface and result in hyperechoic echogenicity formation compared with adjacent tissues. Also, the hyperechoic echogenicity may be caused by the fatty tissue infiltration to the salivary glands.²³ The decrease in echogenicity may also be due to the infiltration of inflammatory cells into the gland.^{19,20} The regular margins in normal salivary glands became irregular after radiotherapy. This irregularity may be a result of

acinar atrophy. However, we did not find any published data regarding this matter.

There have also been very few data evaluating PSV, EDV and RI changes in salivary glands after radiotherapy. In our study, PSV in the parotid and submandibular glands reduced after radiotherapy but the values were insignificant. Ying *et al* reported similar results.⁶ However, they only evaluated PSV for parotid glands. They also found statistically significant values.⁶

No study evaluated submandibular PSV following radiotherapy. In a normal salivary gland, vessels are surrounded by thick granules and acini so that they are not able to impulse. This could be the result of higher PSV values in normal salivary glands. On the other hand, after radiotherapy the destruction of acini lessens the pressure on vessels and reduces the PSV values.⁶ This reduction could also be a result of the increase in arterial venous shunting across the capillary bed that has low amounts of parenchymal tissue.⁶

In our study, EDV values of parotid and submandibular glands decreased in stages I and II but increased in stage III while the PSV values decreased simultaneously. We did not find any statistically significant values. Ying *et al* also reported insignificant differences regarding EDV between parotid glands before and after radiotherapy. EDV changes may be a result of tissue and RI changes after radiotherapy.

We found minimal RI changes after radiotherapy, which were insignificant. Ying *et al* reported that RI values decrease after radiotherapy, which was similar to our findings. This reduction could be a result of acini destruction which leads to removal of pressure from the vessels, the same way as described in PSV.⁶

We also evaluated the effect of age on the sensitivity of salivary glands to radiation. Only PSV and EDV in stage II, gland margins of submandibular glands in stage II and length of submandibular glands in stage III were independent from age. Besides, changes were more

frequent among patients below the age of 49 years. This difference may be owing to the tissue variations between different age groups. Older people have fewer acini that are sensitive to radiation²⁴ and more fatty tissue compared with younger people.²⁵ Thus, salivary glands are more sensitive in the young compared with older people.²⁶

Our results also showed that echotexture and echogenicity of both glands were independent in stage II of sonography, which could be owing to the higher incidence of acute changes and inflammatory reactions in this stage.

We compared all qualitative and quantitative variables between parotid and submandibular glands. Only length in stages I and II and echogenicity in stage III were different between the two glands. Our results were different to those which proposed that the parotid gland is more sensitive than the submandibular gland.^{3,25} Complementary studies to clarify these differences are suggested.

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Conclusion

We concluded that length, width and depth of parotid and submandibular glands reduce during radiotherapy. Also, echotexture, echogenicity and gland margins change to heterogenic, hypoechoic and irregular, respectively, owing to the acini changes and presence of inflammatory procedures.

We also concluded that PSV, EDV and RI values decrease after radiotherapy and younger patients are more sensitive to these changes.

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