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ULTRASOUND HISTOGRAM ASSESSMENT OF PAROTID GLAND INJURY FOLLOWING HEAD-AND-NECK RADIOTHERAPY: A FEASIBILITY STUDY

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Abstract

Xerostomia (dry mouth), resulting from radiation damage to the parotid glands, is one of the most common and distressing side effects of head-and-neck cancer radiotherapy. A noninvasive, objective imaging method to assess parotid injury is lacking, but much needed in the clinic. Therefore, we investigated echo histograms to quantitatively evaluate the morphologic and microstructural integrity of the parotid glands. Six sono-graphic features were derived from the echo-intensity histograms to assess the echogenicity, homogeneity and heterogeneity of the parotid gland: (1) peak intensity value (I_{peak}), (2) -3 -dB intensity width (W_{3-dB}), (3) the low ($<50\%$ I_{peak}) intensity width (W_{low}), (4) the high ($>50\%$ I_{peak}) intensity width (W_{high}), (5) the area of low intensity (A_{low}) and (6) the area of high intensity (A_{high}). In this pilot study, 12 post-radiotherapy patients and seven healthy volunteers were enrolled. Significant differences ($p < 0.05$) were observed in four sonographic features between 24 irradiated and 14 normal parotid glands. In summary, we developed a family of sonographic features derived from echo histograms and demonstrated the feasibility of quantitative evaluation of radiation-induced parotid-gland injury.

Keywords

Xerostomia; Ultrasound; Parotid gland; Radiation toxicity; Echo histogram; Head-and-neck cancer; Sonographic features

INTRODUCTION

Radiotherapy is an important treatment modality for many head-and-neck malignancies (Eisbruch 2002); however, the high dose of radiation required to eradicate tumor cells inevitably causes injury to the surrounding normal tissue (Emami et al. 1991). Among the sequelae of head-and-neck radiotherapy, a reduction in salivary excretion because of parotid-gland injury is of particular clinical concern (Braam et al. 2007; Chao et al. 2001; Eisbruch et al. 2001, 2003; Ying et al. 2007). Studies have shown that over 90% of patients with head-and-neck malignancies develop some degree of xerostomia (dry mouth) post-radiotherapy. Often permanent, xerostomia is associated with oral discomfort, increased

rates of dental caries and oral infection, and difficulty in speaking and swallowing (Braam et al. 2007; Wada et al. 2009).

Few studies have been conducted using ultrasound to assess radiation-induced parotid injuries despite its wide use as a diagnostic tool for parotid neoplasms and infections (Bhatia et al. 2010; Brennan et al. 2011; Howlett 2003; Katz et al. 2009; Sodhi et al. 2011; Yoo et al. 2010). Recently, the Doppler technique and sonographic appearance of the parotid glands were proposed to evaluate post-radiotherapy parotid glands (Cheng et al. 2011a; Imanimoghaddam et al. 2012; Ying et al. 2007). In general, radiation toxicity can be characterized into two categories: acute toxicity (< 3 months post-radiotherapy) and late toxicity (>3 months post-radiotherapy). In a Doppler study of late toxicity (3–8 years post-radiotherapy), significant differences were demonstrated in high peak systolic velocity (PDV), resistive index (RI) and pulsatility index (PI) between the irradiated and healthy parotid glands (Ying et al. 2007). However, no significant differences regarding PDV, end diastolic velocity (EDV) and RI in the parotid glands were found at 2 weeks or 6–7 weeks post-radiotherapy (Imanimoghaddam et al. 2012). Sonographic features of the parotid glands, such as echogenicity, showed significant difference in both late toxicity (Ying et al. 2007) and acute toxicity groups (Imanimoghaddam et al. 2012).

Whereas previous ultrasound studies demonstrated changes in the sonographic appearances of irradiated parotid glands (Cheng et al. 2011a), these studies are mostly qualitative, or at best, semiquantitative. Typically, B-mode images of the parotid glands are interpreted by a clinician; and ultrasound diagnosis is based on the sonographic size, morphology, relative echogenicity and level of homogeneity and heterogeneity. These interpretations of B-mode images are subjective and may not be able to capture subtle changes of the echogenicity. Therefore, the purpose of this study is to investigate sonographic features as potential imaging signatures to quantitatively assess parotid-gland injury in patients with head-and-neck cancer post-radiotherapy. Ultrasound evaluation of irradiated parotid glands will provide information on the morphologic and structural changes of the parotid glands after radiotherapy, which may allow for a better understanding of the cause of xerostomia.

The rest of the article is structured as follows. The Methods section describes the ultrasound scanning of the parotid glands, data analysis procedures and computation of the sonographic features. The Results section compares the sonographic features of irradiated and normal parotid glands. In particular, we demonstrate the inter- and intraobserver reliability of identifying parotid gland contours. The Discussion section addresses the major findings and limitations of this study, and is followed by the Conclusion section.

METHODS

Study participants

In this pilot study, we recruited 19 subjects (12 patients post head-and-neck radiotherapy and seven healthy volunteers). Our ultrasound study was conducted under Emory University's Institutional Review Board approval. Full, written, informed consent was obtained from all participants.

Serving as the control group, the seven healthy volunteers (five men and two women) ranged in age from 27 to 60 years (mean: 47 ± 10 years). For the healthy control group, the exclusion criteria included clinical history of salivary gland diseases and previous radiotherapy to the head-and-neck region.

For the patient group, the 12 patients (nine men and three women) ranged in age from 41 to 72 years (mean: 54.9 ± 8.2 years). All patients had previously received radiation treatment

for their head-and-neck malignancies, such as laryngeal and oropharyngeal cancers. The median radiation dose to the left parotid gland was 30.3 Gy (range: 11.0–63.4 Gy) and to the right parotid gland was 34.4 Gy (range: 21.5–51.4 Gy). The average time elapsed between radiation completion and ultrasound study was 17.2 months (range 12.1–23.9 months). Thus our cross-sectional study is based on late toxicity.

Ultrasound scans of parotid glands

From January to August 2011, each participant underwent one ultrasound study of the bilateral parotid glands. A total of 24 post-radiotherapy and 14 healthy (nonirradiated) parotid glands were analyzed. We established a standardized protocol for ultrasound scanning to facilitate systematic measurements of the parotid glands. Ultrasound studies were performed using a clinical scanner (SonixTouch, Ultrasonix, British Columbia, Canada) with a linear array transducer (L14-5/38 probe, 128 elements). All ultrasound data were acquired with the same settings: 10 MHz center frequency, 1 cm focal length, 3 cm depth, 72% gain, 31 frames per second and 80-dB dynamic range. These settings were determined, based on clinical experience in parotid-gland examinations, by the radiologist (S.T.) and the medical physicist (T.L.).

All ultrasound scans were performed on the bilateral parotids with the transducer positioned longitudinally and the patient in the sitting position. During the ultrasound scan, a thin layer of ultrasound gel was used to ensure good coupling between the face and the ultrasound probe. The probe was placed perpendicular to the scan surface with minimal pressure applied to the face. All B-mode images were saved in 8-bit grey scale—the intensity ranged between 0 and 255. Each B-mode image contained 488×356 pixels; and the size of each pixel was 0.078 mm in the lateral direction and 0.084 mm in the depth (beam) direction.

Ultrasound image analysis with echo-intensity histogram

We proposed to use an echo-intensity histogram method to quantitatively characterize the parotid glands. As shown in Figure 1, an echo histogram presents a graphical distribution of the pixel intensities within the region-of-interest (ROI). The echo histograms and sonographic features used to assess radiation damage to the parotid glands were generated by in-house signal processing software written in MatLab® (Mathworks, Natick, MA, USA).

Our echo histogram method consisted of the following steps:

- *Ultrasound B-mode display and parotid gland contours.* The first step is to display the grayscale ultrasound image. The boundaries of the left and right parotid glands on the B-mode images were manually contoured by a radiologist (S.T.).
- *ROI selection and echo histogram generation.* There are two approaches for the ROI selection. One is to use physicians' contours of the parotid glands. Another is to use a fixed ROI within the physicians' contours of the parotid glands. In this article, a fixed ROI of 3 cm (width) $\times$ 0.5 cm (depth) was used for the analyses. On B-mode images, the ROI was placed in the superficial lobe of the parotid glands. In other words, the ROI was placed on the superficial boundary of the parotid surface, and extended 3 cm in width and 0.5 cm in depth. Each ROI consisted of 2290 pixels (sample points). The histogram of the ROI was subsequently generated.
- *Sonographic features extraction.* As shown in Figure 1, six sonographic features were computed from the histogram to provide additional quantification of the echogenicity and echo-texture of the parotid glands. The I_{peak} is the peak intensity value of the histogram. W_{-3dB} is the $-3dB$ intensity width of the histogram. W_{low} and W_{high} capture the width of the low ($<50\% I_{peak}$) intensity and the high ($>50\% I_{peak}$) intensity, respectively. A_{low} and A_{high} characterize the area under the low

intensity and high intensity curves. These sonographic features provide quantitative measures of the echogenicity (I_{peak}), homogeneity (W_{-3dB}) and heterogeneity (W_{low} , W_{high} , A_{low} and A_{high}) of the parotid gland.

Reliability study

We have conducted a reliability study with ultrasound images of the left and right parotid glands from the first 10 participants (five healthy volunteers and five post-radiotherapy patients). To evaluate interobserver reliability, two observers (one radiologist and one ultrasound physicist) were asked to independently contour the parotid glands on the 20 ultrasound images. Each observer was blinded to the contours and parameter values of the other observer. The variations of the area and depth were calculated for assessment of consistency among measurements by the two observers.

To evaluate intraobserver reliability, one observer (S.T.) was asked to assess 20 ultrasound images of the parotid glands at two time points. The parotid glands were first contoured on all images in September 2011. The same observer was asked to repeat the contours 6 months later. The 6-month time interval between assessments was chosen to reduce recall bias. From these contours, the area of the parotid gland and the depth (skin to the superficial surface of the parotid gland) were calculated. The variations of the parotid area and depth were computed for assessment of consistency among measurements by the same observer.

Statistical analysis

We computed the average echo histograms for the irradiated and normal parotid glands. To gain a fundamental understanding of the intensity distributions, the averaged histograms were curve-fitted with a mathematical model—the summation of Gaussian distributions (Cuadra et al. 2005; Emami et al. 1991; Nelson et al. 2008; Slabaugh et al. 2009). The Gaussian distributions is defined as

$$S(x) = \sum_{n=1}^N A_n \cdot \exp \left(-\left(\frac{x-m_n}{\sigma_n} \right)^2 \right) \quad (1)$$

where x is a variable, parameter m_n is the *mean* (location of the peak), σ_n is the standard deviation, A_n is the amplitude coefficients for the n th Gaussian distribution and N is the number of Gaussian distributions.

The fitting results were further evaluated with an R-squared (R^2) analysis. R^2 is a statistical measure of how well a regression line approximates real data points, where an R^2 of 1.0 (100%) indicates a perfect fit. The R^2 is computed as follows:

$$R^2(X, Y) = \frac{Cov(X, Y)}{\sigma(X) \cdot \sigma(Y)} \quad (2)$$

where X and Y are two variables, Cov represents the covariance and σ is standard deviation.

Statistically, the sonographic features derived from the echo histograms were expressed as means and standard deviations. A paired t -test was used to examine the significance of the difference between post-irradiation and normal parotid gland measurements. A p value of <0.05 was considered to indicate statistical significance.

RESULTS

The parotid glands of all 19 participants were successfully imaged with high-resolution (10 MHz) ultrasound, yielding 38 B-mode images (24 irradiated and 14 normal parotid glands). Figures 2a and b show the ultrasound images of the left and right parotid glands of a healthy volunteer: the images demonstrated homogeneous echo texture and fine soft tissue echogenicity. In contrast, the irradiated parotid glands often revealed heterogeneity on the ultrasound images. Figure 3 shows the B-mode images of the parotid glands of a post-radiotherapy patient. The patient was a 64-year-old woman, diagnosed with stage I invasive laryngeal carcinoma, who received external beam radiation treatment between December 2009 and February 2010. She received 21.5 Gy to the left parotid gland and 63.4 Gy to the right parotid gland. She underwent ultrasound scanning 18 months after treatment completion. Hypoechoic (darker) areas and hyperechoic (brighter) lines or spots are visible on the B-mode images of these parotid glands. She experienced grade I late xerostomia according to the physician's (J.J.B.) clinical assessment.

Interobserver reliability is demonstrated in Figure 4. Between the two observers, the mean percentage difference of the parotid depth was $0.1\% \pm 9.0\%$; and the mean percentage difference of the parotid area was $0.2\% \pm 10.7\%$. Intraobserver reliability was demonstrated in Figure 5. Between the two measurements of the same observer, the mean percentage difference of the parotid depth was $3.0\% \pm 10.0\%$; and the mean percentage difference of the parotid area was $3.0\% \pm 11.6\%$.

We generated the echo histograms and calculated sonographic features for all the participants. Figures 6a and b are the corresponding histograms of the right parotid glands of the healthy volunteer shown in Figure 2, and post-radiotherapy patient shown in Figure 3, respectively. Compared with the normal parotid, the irradiated parotid histogram demonstrated a decreased peak value I_{peak} , broadened curve (increased W_{high} and W_{3-dB}), as well as increased area in the low intensity (A_{low}) and high intensity (A_{high}) regions.

Table 1 depicts the mean and range of 6 sonographic features of the two groups. Statistical analyses confirmed significant differences between post-radiotherapy and normal parotid glands in 4 out of the 6 sonographic features. Figure 7 shows the average sonographic features of the post-irradiation and normal parotid glands, which demonstrated an overall trend of radiation-induced decreases in I_{peak} , A_{low} and W_{low} values, coupled with increases in W_{3dB} , A_{high} and W_{high} . Among the six sonographic features, A_{high} and W_{high} revealed the most significant differences.

Overall, the average histograms of the 24 irradiated and 14 normal parotid glands are shown in Figure 8. To further our understanding of the histogram, we examined mathematical models to fit the irradiated and normal parotid histograms. The average histogram of the normal parotid glands closely conformed to a single Gaussian distribution curve, as shown in Figure 9a. The linear regression analysis (Fig. 9b) and the corresponding R^2 of 0.996 demonstrated excellent curve fitting. For the average histogram of the irradiated parotid glands, the best curve fitting was achieved through the summation of three Gaussian distribution curves, as shown in Figure 10. The corresponding R^2 of 0.999 indicated a near-perfect fit.

DISCUSSION

We have demonstrated the feasibility and reliability of utilizing ultrasonic imaging and echo histograms to assess radiation-induced parotid injury. Ultrasound data from 24 post-radiotherapy parotid glands were compared with those of 14 normal glands using echo-intensity histograms. In this study, significant differences were revealed in four sonographic

features derived from the echo-intensity histograms: peak intensity value (I_{peak}), -3dB intensity width ($W_{-3\text{dB}}$), the high ($>50\%$ I_{peak}) intensity width (W_{high}) and the area of high intensity (A_{high}). In particular, post-radiotherapy parotid glands often have a distribution of brighter lines and spots on the B-mode images, and accordingly, A_{high} and W_{high} showed the highest significance.

Our ultrasound findings were consistent with the previous ultrasound studies (Cheng et al. 2011a; Ying et al. 2007). The sonographic appearance of irradiated parotid glands was characteristically different from the normal glands. Parotid glands of the healthy volunteers tended to be homogenous (Fig. 2), whereas parotid glands in the post-radiotherapy patients were predominantly heterogeneous (Fig. 3). In previous studies, the echogenicity of the parotid glands was assessed and subjectively classified into hypoechoic, isoechoic and hyperechoic compared with the adjacent masseter muscle (Cheng et al. 2011a, 2011b; Howlett 2003; Wu et al. 2011). In the present study, morphologic and structural variations between normal and post-radiotherapy parotid glands were quantified with a family of sonographic features. One advantage of our ultrasound method is its operator independence and objectivity. In addition, our sonographic features could capture subtle changes, which may be difficult to detect through visual inspection.

Histologically, normal parotid glands consist entirely of serous cells - with densely packed translucent secretory granules (Eisbruch 2002; Eisbruch et al. 2003; Grehn et al. 1997; Henriksson et al. 1994; Radfar and Sirois 2003). These densely packed cells and granules provide uniform and highly reflective interfaces for the ultrasound beams (Katz et al. 2009), accounting for the homogeneous and hyperechoic appearance of the normal parotid glands. After irradiation, there is a loss of acini in the parotid gland and the remaining acini become disorganized and larger than normal (Grehn et al. 1997; Nagler 2002). Radiation-induced chronic sialadenitis, with inflammatory infiltrate and fibrosis was also found in the post-irradiation parotid glands (Konings et al. 2006; Radfar and Sirois 2003; Seifert 1995; Teymoortash et al. 2005). The heterogeneous echotexture of post-radiotherapy parotid glands may be due to the presence of patches of inflammatory infiltrate, which appears as multiple hypoechoic areas and the presence of fibrosis, which appears as hyperechoic lines or spots. With the proliferation and fibrosis of the intraparotid ducts, the ducts may become less elastic and compressible hindering excretion of saliva.

Mathematically, Gaussian distributions fitted the histograms of the irradiated and normal parotid glands. The average histogram of the normal parotid glands exhibited a single Gaussian distribution (Fig. 9), whereas the irradiated parotid glands exhibited a combination of three Gaussian distributions (Fig. 10). The histogram of the normal parotid glands is a single Gaussian distribution because normal parotid glands have single cell type. The histogram of post-radiotherapy parotid glands is often a combination of three Gaussian distributions because of the morphologic and structural changes induced by radiation. The center Gaussian curve (G_1) corresponds to the histogram of normal parotid gland. The peak intensity of G_1 (68.1) of the post-radiotherapy parotid glands is close to that of the normal ones (79.3). In addition, the -3dB widths are similar, the former is 30.5 and the latter is 26.6. The second Gaussian (G_2) corresponds to the hyperechoic part of the histogram, which mainly results from the post-radiotherapy fibrotic changes of the parotid ducts. The third Gaussian (G_3) corresponds to the hypoechoic part of the histogram, which is mainly related to radiation-induced chronic sialadenitis. The inflammatory infiltrate could lower the echogenicity of the parotid glands, leading to decreased echogenicity in post-radiotherapy glands (Radfar and Sirois 2003; Teymoortash et al. 2005).

This pilot study has several limitations, including the small sample size. Nevertheless, the feasibility of ultrasound to evaluate radiation-induced injury to the parotid gland is

demonstrated. Second, ultrasound pixel intensity histograms are highly dependent on the scanner and its setting. For example, the peak intensity value (I_{peak}) will vary with the gain and the ROI depth. Therefore, we used the same ultrasound scanner with standardized settings throughout the study. With the use of raw radio-frequency echo data and proper calibration, this limitation could be overcome. Third, post-irradiation parotid glands were compared with normal ones, however, the radiation dose delivered to individual parotid gland was not considered. Radiation dose is an important factor in predicting radiation-induced parotid injury (Blanco et al. 2005; Chao et al. 2001; Deasy et al. 2010; Li et al. 2007). We have embarked on a large-scale clinical study to further develop our ultrasound technology in assessing radiation-induced parotid-gland injury, to understand radiation dose response of the parotid glands and to correlate parotid gland injury to the clinical endpoint (dry mouth).

CONCLUSIONS

To better diagnose and understand xerostomia in head-and-neck cancer radiotherapy, we have developed a family of sonographic features that provide quantitative evaluation of the morphologic changes and the architectural integrity of the post-irradiation parotid glands. In this “proof of principle” *in vivo* study, significant differences in sonographic features were demonstrated between irradiated and normal parotid glands. These objective, quantitative sonographic features could provide complementary diagnostic information to the current clinical examination.

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References

- Bhatia KSS, Rasalkar DD, Lee YP, Wong KT, King AD, Yuen HY, Ahuja AT. Evaluation of real-time qualitative sonoelastography of focal lesions in the parotid and submandibular glands: Applications and limitations. *Eur Radiol.* 2010; 20:1958–1964. [PubMed: 20407904]
- Blanco AI, Chao KS, El Naqa I, Franklin GE, Zakarian K, Vicic M, Deasy JO. Dose-volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005; 62:1055–1069. [PubMed: 15990009]
- Braam PM, Roesink JM, Raaijmakers CP, Busschers WB, Terhaard CH. Quality of life and salivary output in patients with head-and-neck cancer five years after radiotherapy. *Radiat Oncol.* 2007; 2:3. [PubMed: 17207274]
- Brennan, PA.; Herd, MK.; Howlett, DC.; Gibson, D.; Oeppen, RS. Is ultrasound alone sufficient for imaging superficial lobe benign parotid tumours before surgery?. *Br J Oral Maxillofac Surg.* 2011. E-pub ahead of print, doi: <http://dx.doi.org/10.1016/j.bjoms.2011.01.018>
- Chao KSC, Deasy JO, Markman J, Haynie J, Perez CA, Purdy JA, Low DA. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: Initial results. *Int J Radiat Oncol Biol Phys.* 2001; 49:907–916. [PubMed: 11240231]
- Cheng SC, Ying MT, Kwong DL, Wu VW. Sonographic appearance of parotid glands in patients treated with intensity-modulated radiotherapy or conventional radiotherapy for nasopharyngeal carcinoma. *Ultrasound Med Biol.* 2011a; 37:220–230. [PubMed: 21208735]
- Cheng SCH, Wu VWC, Kwong DLW, Ying MTC. Assessment of post-radiotherapy salivary glands. *Br J Radiol.* 2011b; 84:393–402. [PubMed: 21511748]
- Cuadra MB, Cammoun L, Butz T, Cuisenaire O, Thiran JP. Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images. *IEEE Trans Med Imaging.* 2005; 24:1548–1565. [PubMed: 16350916]

- Deasy JO, Moiseenko V, Marks L, Chao KSC, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. *Int J Radiat Oncol Biol Phys.* 2010; 76:S58–S63. [PubMed: 20171519]
- Eisbruch A. Clinical aspects of IMRT for head-and-neck cancer. *Med Dosim.* 2002; 27:99–104. [PubMed: 12074474]
- Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2001; 50:695–704. [PubMed: 11395238]
- Eisbruch A, Rhodus N, Rosenthal D, Murphy B, Rasch C, Sonis S, Scarantino C, Brizel D. How should we measure and report radiotherapy-induced xerostomia? *Semin Radiat Oncol.* 2003; 13:226–234. [PubMed: 12903012]
- Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* 1991; 21:109–122. [PubMed: 2032882]
- Grehn AL, Gustafsson H, Franzen L, Thornell LE, Henriksson R. Ultra-structural morphometry of parotid acinar cells following fractionated irradiation. *Oral Oncol.* 1997; 33:23–28. [PubMed: 9192549]
- Henriksson R, Frojd O, Gustafsson H, Johansson S, Yi-Qing C, Franzen L, Bjermer L. Increase in mast cells and hyaluronic acid correlates to radiation-induced damage and loss of serous acinar cells in salivary glands: The parotid and submandibular glands differ in radiation sensitivity. *Br J Cancer.* 1994; 69:320–326. [PubMed: 8297728]
- Howlett DC. High resolution ultrasound assessment of the parotid gland. *Br J Radiol.* 2003; 76:271–277. [PubMed: 12711649]
- Imanmoghadam, M.; Rahrooh, M.; Tafakhori, Z.; Zahedanaraki, S.; Homaeieshandiz, F. Changes of parotid and submandibular glands caused by radiotherapy—An ultrasound evaluation. *Dentomaxillofac Radiol.* 2012. E-pub ahead of print, doi: <http://dx.doi.org/10.1259/dmfr/17113005>
- Katz P, Hartl DM, Guerre A. Clinical ultrasound of the salivary glands. *Otolaryngol Clin North Am.* 2009; 42:973–1000. [PubMed: 19962004]
- Konings AWT, Faber H, Cotteleer F, Vissink A, Coppes RP. Secondary radiation damage as the main cause for unexpected volume effects: A histopathologic study of the parotid gland. *Int J Radiat Oncol Biol Phys.* 2006; 64:98–105. [PubMed: 16226398]
- Li Y, Taylor JM, Ten Haken RK, Eisbruch A. The impact of dose on parotid salivary recovery in head and neck cancer patients treated with radiation therapy. *Int J Radiat Oncol Biol Phys.* 2007; 67:660–669. [PubMed: 17141973]
- Nagler RM. The enigmatic mechanism of irradiation-induced damage to the major salivary glands. *Oral Dis.* 2002; 8:141–146. [PubMed: 12108758]
- Nelson TR, Cervino LI, Boone JM, Lindfors KK. Classification of breast computed tomography data. *Med Phys.* 2008; 35:1078–1086. [PubMed: 18404942]
- Radfar L, Sirois DA. Structural and functional injury in minipig salivary glands following fractionated exposure to 70 Gy of ionizing radiation: An animal model for human radiation-induced salivary gland injury. *Oral Surg Oral Med O.* 2003; 96:267–274.
- Seifert G. Etiology and differential diagnosis of sialadenitis. *Laryngorhinootologie.* 1995; 74:274–281. [PubMed: 7605565]
- Slabaugh G, Unal G, Wels M, Fang T, Rao B. Statistical region-based segmentation of ultrasound images. *Ultrasound Med Biol.* 2009; 35:781–795. [PubMed: 19152999]
- Sodhi KS, Bartlett M, Prabhu NK. Role of high resolution ultrasound in parotid lesions in children. *Int J Pediatr Otorhinolaryngol.* 2011; 75:1353–1358. [PubMed: 21816492]
- Teymoortash A, Simolka N, Schrader C, Tiemann M, Werner JA. Lymphocyte subsets in irradiation-induced sialadenitis of the submandibular gland. *Histopathology.* 2005; 47:493–500. [PubMed: 16241997]
- Wada A, Uchida N, Yokokawa M, Yoshizako T, Kitagaki H. Radiation-induced xerostomia: Objective evaluation of salivary gland injury using MR sialography. *Am J Neuroradiol.* 2009; 30:53–58. [PubMed: 18842755]

- Wu VWC, Ying MTC, Kwong DLW. Evaluation of radiation-induced changes to parotid glands following conventional radiotherapy in patients with nasopharyngeal carcinoma. *Br J Radiol.* 2011; 84:843–849. [PubMed: 21224300]
- Ying M, Wu VWC, Kwong DLW. Comparison of sonographic appearance of normal and post-radiotherapy parotid glands: A preliminary study. *Ultrasound Med Biol.* 2007; 33:1244–1250. [PubMed: 17466447]
- Yoo DS, Wong TZ, Brizel DM. The role of adaptive and functional imaging modalities in radiation therapy: Approach and application from a radiation oncology perspective. *Semin Ultrasound Ct.* 2010; 31:444–461.

Fig. 1.
Diagram of an echo histogram and corresponding sonographic features.

Fig. 2. Ultrasound B-mode images of normal parotid glands. Ultrasound images of left (a) and right (b) parotid glands of a 40-year-old healthy volunteer, revealing homogeneous echo texture and fine soft tissue echogenicity.

Fig. 3. Ultrasound B-mode images of post-radiotherapy parotid glands. Ultrasound images of left (a) and right (b) parotid glands of a 60-year-old laryngeal cancer patient, 18 months post-radiotherapy. Hypoechoic areas (arrowheads) and hyper-echoic lines (arrows) are shown in irradiated parotid glands.

Fig. 4.

Interobserver reliability was demonstrated by the agreement between two observers' parotid contours. (a) Depths of the parotid glands based on the contours drawn by the two observers. (b) Areas of the parotid glands based on the contours drawn by the two observers. (P = patient; V = volunteer; L = left; R = right).

Fig. 5. Intra-observer reliability was demonstrated by the agreement between two sets of parotid contours drawn by one observer. (a) Depths of the parotid glands based on the two sets of contours drawn by one observer. (b) Areas of the parotid glands based on the repeated contours by the same observer. (P = patient; V = volunteer; L = left; R = right).

Fig. 6. Echo histograms of normal and irradiated parotid glands. (a) Histogram of the normal right parotid gland shown in Figure 2. (b) Histogram of the irradiated right parotid gland shown in Figure 3.

Fig. 7.
Average sonographic features of the irradiated (in red) and normal (in blue) parotid glands.

Fig. 8. Average histograms of the 24 irradiated (in red) and 14 normal (in blue) parotid glands.

Fig. 9.

(a) Average histogram for normal parotid glands fits a Gaussian distribution curve. (b) The correlation plot between normal parotid data and the Gaussian fitting indicate a high correlation.

Fig. 10.

(a) Comparison of fitting three Gaussian distribution curves with averaged histograms in irradiated patients and their correlation plots. (b) The correlation plot between irradiated parotid data and the summation of the three Gaussian fitting indicate a high correlation.

Table 1

Sonographic features of the irradiated and normal parotid glands

Groups/parameters	I _{peak}	W _{-3dB}	A _{low}	A _{high}	W _{low}	W _{high}
Post-RT parotid (mean, range)	55.6 (27.0–90.0)	50.0 (31.0–67.0)	4.0 (2.1–7.7)	16.2 (12.1–26.9)	27.3 (12.0–52.0)	143.7 (102.0–203.0)
Normal parotid (mean, range)	77.3 (56.0–88.0)	36.3 (23.0–46.0)	4.7 (3.2–5.8)	7.1 (3.1–10.4)	32.9 (19.0–42.0)	72.5 (31.0–93.0)
<i>p</i> value	<0.001	<0.001	=0.184	<0.001	=0.064	<0.001