Diagnostic Accuracy of Ultrasonic Histogram Features to Evaluate Radiation Toxicity of the Parotid Glands:

A Clinical Study of Xerostomia Following Head-and-Neck Cancer Radiotherapy

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Rationale and Objectives: To investigate the diagnostic accuracy of ultrasound histogram features in the quantitative assessment of radiation-induced parotid gland injury and to identify potential imaging biomarkers for radiation-induced xerostomia (dry mouth)—the most common and debilitating side effect after head-and-neck radiotherapy (RT).

Materials and Methods: Thirty-four patients, who have developed xerostomia after RT for head-and-neck cancer, were enrolled. Radiation-induced xerostomia was defined by the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer morbidity scale. Ultrasound scans were performed on each patient's parotids bilaterally. The 34 patients were stratified into the acute-toxicity groups (16 patients, ≤3 months after treatment) and the late-toxicity group (18 patients, >3 months after treatment). A separate control group of 13 healthy volunteers underwent similar ultrasound scans of their parotid glands. Six sonographic features were derived from the echo-intensity histograms to assess acute and late toxicity of the parotid glands. The quantitative assessments were compared to a radiologist's clinical evaluations. The diagnostic accuracy of these ultrasonic histogram features was evaluated with the receiver operating characteristic (ROC) curve.

Results: With an area under the ROC curve greater than 0.90, several histogram features demonstrated excellent diagnostic accuracy for evaluation of acute and late toxicity of parotid glands. Significant differences ($P < .05$) in all six sonographic features were demonstrated between the control, acute-toxicity, and late-toxicity groups. However, subjective radiologic evaluation cannot distinguish between acute and late toxicity of parotid glands.

Conclusions: We demonstrated that ultrasound histogram features could be used to measure acute and late toxicity of the parotid glands after head-and-neck cancer RT, which may be developed into a low-cost imaging method for xerostomia monitoring and assessment.

Key Words: Xerostomia; ultrasound; parotid gland; radiation toxicity; sonographic features.

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Xerostomia (dry mouth) is a common, often permanent, and debilitating morbidity of radiotherapy (RT) for head-and-neck malignancies (1,2). Patients with severe xerostomia have thick secretions, difficulty in swallowing and speaking, and are at high risk for oral infection and dental caries (3). This symptom burden impairs the quality of life (QoL) of many head-and-neck cancer survivors for months, even years, after treatment (4). It is well established that the main cause of RT-induced xerostomia is irradiation of parotid glands—the major salivary glands producing ~60% of total saliva (1). Recent clinical studies indicate that intensity-modulated radiotherapy (IMRT) provides a significant advantage in sparing the parotid glands

and reducing xerostomia. However, even with the new technology, 17%–30% of patients treated with IMRT still develop permanent xerostomia. There is substantial heterogeneity in parotid gland injury after radiation (5–7).

In the clinic, radiation-induced xerostomia is assessed using patient-based or physician-based grading systems. For example, the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) established a morbidity scale to evaluate post-RT salivary glands. Specifically, salivary gland toxicity was divided into two categories: acute (≤3 months after RT) toxicity and late (>3 months after RT) toxicity. Physicians assign a score of grade 1 (slight dryness) to grade 4 (necrosis or fibrosis) for acute or late salivary toxicity (8). Such subjective measures of radiation toxicity are prone to intraobserver and interobserver variability. In recent years, many groups have been investigating imaging technologies to evaluate parotid gland injury induced by radiation. Studies using computed tomography (CT), magnetic resonance imaging (MRI), MR sialography, and single-photon emission computed tomography scintigraphy have shown some degree of success in assessing the severity of parotid gland injury and documenting normal tissue response to RT (9–17). However, the high cost, the technical complexity, and the need for dedicated imaging expertise (CT, MRI, or nuclear medicine) preclude their use in routine clinical assessment of xerostomia.

The concept of ultrasound imaging to evaluate parotid gland injury is especially attractive because ultrasound is safe, portable, widely available, easy to use, and cost effective. In particular, because parotid glands are superficial structures wrapping around the mandible, they are readily amenable to ultrasound examination. Ultrasound, therefore, is the standard imaging modality in the assessment of salivary gland diseases such as neoplasms, Sjogren syndrome, sialadenitis, and sialolothiasis. However, there is limited information in the literature about evaluation of radiation-induced parotid gland injury or xerostomia using ultrasound (9). Previously, we have proposed an ultrasound technology based on quantitative analysis of echo-intensity histogram to assess RT-associated parotid gland injury (18). A family of sonographic features was derived from the echo histogram to quantify the echogenicity and heterogeneity of parotid glands, which is used to assess the morphologic and architectural integrity of post-RT parotids. In a pilot study of 12 patients, we demonstrated the clinical feasibility of using these echo histogram features in evaluating parotid gland toxicity after RT (18).

Another appealing factor of ultrasound histogram evaluation of RT-related parotid gland toxicity is that it could eliminate variations in subjective radiologic interpretations of ultrasound images. To further explore this ultrasound technology in the evaluation of RT-induced parotid gland injury, we embarked on this clinical study. The primary objective was to determine the diagnostic accuracy of echo-intensity histogram parameters in the assessment of RT-induced parotid gland injury. In addition, we compared the quantitative ultrasound examination with radiologists' evaluation of acute and late toxicities of RT to parotid glands. Special emphasis was placed on acute toxicity for patients within 3 months of cancer treatment. We want to emphasize the importance of developing safe and easy ultrasound technology to detect acute toxicity because early detection of parotid gland injury could enable early interventions to minimize long-term morbidity.

MATERIALS AND METHODS

Study Population

The study was approved by our institutional review board and in compliance with the Health Insurance Portability and Accountability Act. The eligibility criteria for post-RT patients included 1) patients aged ≥18 years; 2) biopsy-confirmed histologic diagnosis of squamous cell carcinoma of oropharynx, hypopharynx, larynx, or patients with unknown primary tumor with unilateral metastases to neck lymph nodes; 3) radiation volume ≥80% of major salivary glands (parotids) and ≥27 Gy delivered to parotid glands; 4) no salivary gland malignancy; 5) no salivary gland disease, for example, Sjogren syndrome; and 6) clinically confirmed xerostomia based on the RTOG/EORTC acute- and late-toxicity scoring scheme. We have also enrolled a normal control group, and the eligibility criteria for healthy volunteers included 1) participants aged ≥18 years; 2) no prior RT or surgery to head and neck for any reason; 3) no prior malignancies or chemotherapy; 4) no salivary gland malignancy; and 5) no salivary gland disease, for example, Sjogren syndrome.

We stratified our post-RT patients into the acute-toxicity and late-toxicity groups. In general, radiation toxicity is divided into two categories: acute (early) and chronic (late) toxicity (19). Acute toxicity is defined as toxicity occurring within the first 3 months of treatment completion, whereas late toxicity is defined as toxicity occurring beyond 3 months after treatment. RT-induced salivary injury is a complex process and evolves through phases (8). During the early course of RT (often 4–6 weeks), most patients may experience acute salivary gland swelling and pain. A reduction in salivary function can begin within 1 week of RT and usually persists afterward (20). For some patients, salivary function gradually recovers within 1–2 years after RT. And for others, acute salivary toxicity may progress to chronic radiation-induced sialadenitis and fibrosis.

Ultrasound Imaging Protocol

As described in previous reports, we established a standardized protocol for ultrasound scanning to facilitate quantitative evaluation of parotid glands (18,21). In brief, 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 B-mode images were acquired with the same settings: 10-MHz center frequency, 1.00-cm focal length, 3-cm depth, 72% gain, 31 frames per second, and 80-dB dynamic range.

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