Objective: To explore the application of parotid R2* values for evaluating Sjögren syndrome (SS).

Methods: Twenty-four consecutive SS patients and 24 sex-matched and age-matched healthy volunteers underwent bilateral parotid 3.0 T magnetic resonance (MR) imaging, including blood oxygenation level dependent sequence. Parotid R2* values of SS patients and volunteers were compared. A receiver operating characteristic analysis was used to evaluate the diagnostic performance of parotid R2* value alone and in combination with MR nodular grade.

Results: The left parotid R2* value was significantly lower than the right (P = 0.006) in SS patients. Parotid R2* value in SS patients was significantly lower than that in healthy volunteers (P < 0.001). With a cutoff value of 64.14/s, the sensitivity of the parotid R2* value was 62.5% in the diagnosis of SS. By combining R2* value with MR nodular grade, the sensitivity reached 87.5%.

Conclusions: Parotid R2* value contributed to the diagnosis of Sjögren syndrome combined with MR nodular grade.

Key Words: R2* values, Sjögren syndrome, Parotid gland, Magnetic resonance image

From the Departments of †Radiology and ‡Rheumatology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing; †Philips Healthcare, Shanghai; and ‡Philips Healthcare, Hong Kong, PR. China. Received for publication May 27, 2016; accepted August 11, 2016.

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Sjögren syndrome (SS) is a chronic systemic autoimmune disease that usually affects women older than 40 years. It can be an isolated syndrome (primary SS) or associated with other autoimmune disorders (secondary SS). Sjögren syndrome is characterized by the injury of the exocrine glands, with clinical manifestations of salivary gland enlargement, xerostomia, and keratoconjunctivitis. The parotid glands, which produce 60% to 65% of the total saliva in normal conditions, are most frequently involved in SS. Histological analysis of parotid glands typically reveals loss of normal gland architecture, lymphocytic and plasma cell infiltration, and secretory dysfunction. Hence, evaluating the degree of injury of the parotid glands plays an important role in the assessment of SS.

Conventional X-ray sialography is most commonly used in the diagnosis of SS, which clearly shows ductal systems. However, this methodology requires dilatation of the duct and carries the risk of iodine allergy. Ultrasonography and computed tomography could reflect the texture of the gland tissues noninvasively. However, their assessment is qualitative rather than quantitative, and computed tomography involves ionizing radiation. 99mTcTechnetium pertechnetate sialography could evaluate salivary gland function of both secretory and excretory cells with exposure to radionuclides, although accurate morphological evaluation is impossible. Other methods, such as salivary flow rate and component measurements, are complex and only auxiliary.

Magnetic resonance (MR) imaging is noninvasive, radiation-free, and sensitive to the morphological and signal changes of parotid glands. The MR sialography could evaluate the parotid ductal system noninvasively without using any contrast agents. Further, various functional MR techniques, such as diffusion weighted imaging MR imaging, MR spectroscopy, and intravoxel incoherent motion MR imaging have been utilized in the evaluation of parotid glands. For example, the apparent diffusion coefficient (ADC) values of parotid glands increased at early-stage SS and decreased in advanced diseases.

Sjögren syndrome is a complex and progressive disease, and the parotid injury grade could be assessed based on conventional MR images, as shown in Table 1. However, this assessment was qualitative and usually insensitive to early stage SS. T2* mapping has been widely applied in various physiologic and pathologic conditions. Recently, quantitative T2* measurement allows high resolution of thin cartilage layers and quantitative grading of cartilage degeneration. In addition, R2* (1/T2*), to a degree, could reflect the change of blood oxygen content in brain and kidney. Neural activation increases regional cerebral blood flow and concomitantly increases venous blood oxygenation. The R2* value of the remaining kidney decreased due to increased oxygen content in both the medulla and cortex after nephrectomy with the effect of increased glomerular volume and capillary volume.

To the best of our knowledge, no T2* mapping study on parotid injury in SS patients has been previously reported. In the head and neck region, T2* value is usually short due to the inhomogeneous magnetic field, and affected by many factors. By using a fast field echo sequence, the parotid T2* mapping could be obtained with a short scan time and high signal-to-noise ratio. Simon-Zoula et al reported that the parotid T2* value rose initially and then recovered slowly after acid stimulation in healthy volunteers. The initial increase could be a consequence of decreased oxygenation attributed to the secretion of stored saliva by the glands. And the subsequent decrease in R2* indices may correspond to the gradual resupply of oxygen and gland perfusion during the production of new saliva. Patients with SS suffered from a redox imbalance state due to oxidative stress (OS).
TABLE 1. Parotid Injury in Sjögren Syndrome According to Makula et al’s Scale

<table>
<thead>
<tr>
<th>Grading</th>
<th>Appearance in Magnetic Resonance Imaging</th>
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<tbody>
<tr>
<td>Grade 0</td>
<td>Normal homogeneous gland parenchyma</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Fine reticular or small nodular structure, diameter of nodules &lt; 2 mm</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Medium nodular pattern, diameter of nodules 2–5 mm</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Coarsely nodular, diameter of nodules &gt; 5 mm</td>
</tr>
</tbody>
</table>

which might be reflected with T2* mapping. Thus, the purpose of this study was to compare the difference in parotid R2* values between SS patients and healthy volunteers and to explore the role of parotid R2* values for the assessment of SS.

MATERIALS AND METHODS

Subjects
The study protocol was approved by the ethical committee of Nanjing Drum Tower Hospital, and written informed consent was obtained from each subject. From January 2015 to January 2016, 24 patients (22 women and 2 men; age range, 18–68 years; mean age, 46.95 ± 15.92 years) with SS were consecutively and prospectively enrolled in this study. Patients with SS should meet the revised international classification criteria for SS (see Appendix, Supplemental Digital Content 1, http://links.lww.com/JCT/AS58).

Among the 24 patients with SS, 20 had primary disease and 4 had secondary SS associated with systemic lupus erythematosus (3 patients) or rheumatoid arthritis (1 patient). All patients with SS showed positive findings of parotid sialography, indicating parotid gland involvement. No patient received any treatment for SS before MR examination.

Twenty-four age-matched and sex-matched healthy volunteers (22 women and 2 men; age range, 18–68 years; mean age, 46.95 ± 15.92 years) were enrolled as controls. Healthy controls exhibited no symptoms, signs, or histories of mouth, eye or salivary gland problems; no history of radiation treatment of the head and neck; no history of hepatitis C virus infection; no acquired immunodeficiency disease; no lymphoma; no sarcoidosis; and no history of medication use, including diuretics, tricyclic antidepressants, and anticholinergic agents. All healthy volunteers were non-smokers without diabetes.

MR Examination
All subjects were asked to fast from food and drink for at least two hours before the MR examination. All participants were scanned on a 3.0 T MR scanner (Ingenia; Philips Medical Systems, Best, the Netherlands) with a 16-channel head and neck coil. The participants were scanned in the supine position with head first. Scan sequences included axial T1 weighted (T1W) imaging, T2 weighted (T2W) imaging, axial and coronal fat-suppressed T2W imaging as well as blood oxygenation level dependent (BOLD) imaging. Parallel transmission technology was performed in radio frequency field (B1). The volume shimming technology was used to ensure the uniformity of the main magnetic field (B0) to reduce the impact of other factors on the T2* measurement. The scan ranged from the skull base to the submandibular glands, which covered the entire volume of the bilateral parotid glands. The participants were asked to minimize swallowing. The parameters of the scan sequences were shown in Table 2. The entire MR scanning lasted approximately 14 minutes and 30 seconds. All participants underwent MR imaging successfully without any side effect or discomfort.

Image Analysis
All MR images were transmitted into the workstation (Extended MR WorkSpace 2.6.3.5; Philips Medical Systems). Two radiologists (J.H., Z.Y.Z.) with 2 and 10 years of experience in head and neck radiology, respectively, who were blinded to the clinical information judged the degree of parotid injury independently based on MR images according to Makula et al’s scale as Table 1.

In this study, grade 0 was deemed free of injury, whereas grades 1 to 3 were treated as parotid injury, indicating SS. Consensus was reached by consulting a third senior radiologist if there was disagreement between the 2 radiologists.

The BOLD MR images were loaded into SPIN software (Magnetic Resonance Innovations Inc., Detroit, Mich) on a personal computer. Parotid T2* mapping was automatically generated with the previously described method. The BOLD MR images with an echo time (TE) of 4 ms were selected for a clearer demonstration of bilateral parotid structures. The axial slice, which showed the largest area of the parotid glands, was chosen. The region of interest (ROI) was manually drawn in this slice to cover as much of the parotid glands as possible (mean area, 4.08 cm²; range, 2.21–6.70 cm²). The ROI was drawn carefully along the edge of the gland to avoid the retromandibular vein and external carotid artery within the gland. The ROI was automatically copied to the corresponding T2* mapping, and the parotid T2* value was obtained. Then, the parotid R2* value was calculated as follows: R2* = 1/T2*.

Short-term and long-term reproducibility, both inter-rater and intra-rater, was assessed using intraclass correlation coefficient (ICC). The bilateral parotid glands of one subject were measured separately. Two radiologists measured the unilateral parotid gland three times independently, and the averaged value of the three measurements by the 2 radiologists was calculated. Repeated measurement was performed by the 2 radiologists after four weeks for intraobserver and interobserver agreement analyses.

Statistical Analysis
The sensitivity, specificity, and accuracy of the conventional MR imaging in the diagnosis of parotid injury in patients with SS were determined. All the R2* data were in normal distribution by the Shapiro–Wilkinson test. A paired sample t test was used to compare the R2* values of the bilateral parotid glands in volunteers and SS patients. A 2-independent samples t test was used to compare the parotid R2* values between the SS patients and healthy volunteers. Receiver operating characteristic analysis was applied to assess the diagnostic performance of the parotid R2* value in diagnosis. Cutoff values were established by calculating the maximal Youden index (Youden index = sensitivity + specificity − 1). The Spearman rank correlation was used to evaluate the correlation between the MR gland nodule grade and R2* values. The κ coefficient was used to evaluate the interobserver agreement for the MR gland nodule grade. Additionally, an ICC was adopted to evaluate the intraobserver and interobserver agreement for the measurements of the parotid R2* value. SPSS 13.0 (SPSS Inc, Chicago, III) was used for statistical analysis, and P < 0.05 was considered statistically significant.

RESULTS
The MR morphological classification of all parotid glands of the 24 healthy volunteers was grade 0 (Fig. 1A). The MR morphological classification of the bilateral parotid glands in the 24 SS
patients was consistent between the 2 radiologists. There were 11, 5, 3, and 5 SS patients in grade 0, 1, 2, and 3, respectively. By considering grade 0 negative and grades 1 to 3 positive for SS (Fig. 1C), the sensitivity and specificity of the MR morphological diagnosis were 54.17% and 100%, respectively.

There was no significant difference in the R2* values between the bilateral parotid glands (left, 72.16 ± 4.49/s; right, 72.12 ± 6.93/s; P = 0.973) in the 24 healthy volunteers (Fig. 1B). The R2* values of the left parotid glands (64.03 ± 7.91/s) were significantly lower than the right glands (68.50 ± 7.89/s) in the 24 SS patients (P = 0.006) (Fig. 1D). The averaged R2* value of the bilateral parotids was calculated (72.14 ± 5.02/s; range, 64.90–85.68/s) as the representative value of healthy volunteers. The lower R2* value of the bilateral parotids was taken as the representative value of SS patients (64.03 ± 7.91/s; range, 48.28–76.90/s). The R2* value of SS patients was significantly lower than that of healthy volunteers (P < 0.001) (Figs. 1B and D). Receiver operating characteristic analysis showed that with a cutoff value of 64.14/s the sensitivity and specificity of the R2* value was 62.5% and 100%, respectively, in the diagnosis of SS (area under the curve, 0.764; 95% confidence interval [CI], 0.619–0.908) (Fig. 2). The scatter plots of bilateral parotid R2* values in healthy volunteers and SS patients are shown in Figure 3.

With this cutoff of R2* value, 8 of 11 patients with negative MR morphological findings could be diagnosed as having SS (Figs. 1E and F). A combination of MR morphological analysis with the R2* value reached a sensitivity of 87.5% and a specificity of 100% in the diagnosis of SS.

### TABLE 2. Magnetic Resonance Imaging Sequences Parameters for Bilateral Parotid Glands in Patients with Sjögren Syndrome

<table>
<thead>
<tr>
<th>Sequences</th>
<th>T1WI (TSE)</th>
<th>T2WI (TSE)</th>
<th>T2WI (STIR)</th>
<th>T2W (STIR)</th>
<th>BOLD (FFE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging plane</td>
<td>Transverse</td>
<td>Transverse</td>
<td>Transverse</td>
<td>Coronal</td>
<td>Transverse</td>
</tr>
<tr>
<td>TR, ms</td>
<td>400–675</td>
<td>2500–3500</td>
<td>3000</td>
<td>1500–2500</td>
<td>100</td>
</tr>
<tr>
<td>TE, ms</td>
<td>18</td>
<td>20</td>
<td>21</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>TSE factor</td>
<td>8</td>
<td>20</td>
<td>21</td>
<td>25</td>
<td>—</td>
</tr>
<tr>
<td>Matrix</td>
<td>276 × 215</td>
<td>276 × 215</td>
<td>276 × 212</td>
<td>200 × 309</td>
<td>124 × 99</td>
</tr>
<tr>
<td>Slice thickness, mm</td>
<td>4.25</td>
<td>4.25</td>
<td>4.25</td>
<td>4.25</td>
<td>4</td>
</tr>
<tr>
<td>Slice gap, mm</td>
<td>Default</td>
<td>Default</td>
<td>Default</td>
<td>Default</td>
<td>1.5</td>
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<tr>
<td>Slices</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>FOV, mm²</td>
<td>240 × 240</td>
<td>240 × 240</td>
<td>240 × 240</td>
<td>200 × 316</td>
<td>250 × 250</td>
</tr>
<tr>
<td>Voxel size, mm²</td>
<td>0.65 × 0.75</td>
<td>0.45 × 0.50</td>
<td>0.60 × 0.69</td>
<td>1.0 × 0.94</td>
<td>2 × 2.5</td>
</tr>
<tr>
<td>NSA</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>FA, degrees</td>
<td>90</td>
<td>90</td>
<td>120</td>
<td>140</td>
<td>27</td>
</tr>
<tr>
<td>Bandwidth, Hz/Px</td>
<td>287.9</td>
<td>217.6</td>
<td>228.1</td>
<td>437.1</td>
<td>1768.3</td>
</tr>
<tr>
<td>Total scan duration</td>
<td>2 min, 15 s</td>
<td>4 min, 6 s</td>
<td>3 min, 3 s</td>
<td>4 min, 15 s</td>
<td>37 s</td>
</tr>
</tbody>
</table>

TSE indicates turbo spin echo; STIR, short-time inversion recovery; FFE, fast field echo; TR, repeated time; FOV, field of view; NSA, number of signals averaged; FA, flip angle; Px, pixel.

**FIGURE 1.** Axial T1 weighted image shows bilateral parotid glands with homogenous signal intensity in a 53-year-old female healthy volunteer (A). Corresponding BOLD MR image R2* mapping (B) shows a uniform R2* value of bilateral parotid glands (left, 71.63/s; right, 72.77/s). Axial T1 weighted image shows the nodular appearance of bilateral parotid glands (left, grade 2; right, grade 2) in a 53-year-old woman diagnosed with Sjögren syndrome (C). Corresponding BOLD MR image/R2* mapping shows asymmetric R2* values of bilateral parotid glands (left, 61.41/s; right, 80.29/s, left < the cutoff value of 64.14/s) (D). The axial T1 weighted image shows bilateral parotid glands with homogenous signal intensity in a 65-year-old woman diagnosed with Sjögren syndrome (E). Corresponding BOLD MR image/R2* mapping shows symmetric R2* values of bilateral parotid glands (left, 63.38/s; right, 61.51/s), which are both lower than the cutoff value of 64.14/s (F).
The R2* value of parotid glands in patients with SS was significantly lower than that in healthy volunteers, with a mean difference rate of 12.67%. The R2* value generated from BOLD MR imaging, which to a degree could be positively correlated with the content of paramagnetic deoxyhemoglobin and negatively with the blood partial pressure of oxygen, could reflect the partial pressure of oxygen of living tissues both indirectly and noninvasively. The prooxidant state of the patients related to oxidative stress (OS), which is involved with decreased expression of antioxidant activity in conjunctival epithelial cells. The T2* value was also affected by many factors, particularly in the region of the head and neck, where the T2* decay time is relatively short. However, in this study, parallel transmission technology was performed in radio frequency field (B1) and the volume shimming technology was used to ensure the B0 field uniformity to reduce the influence of other factors on the T2* measurement.

Roberts et al15 found that the dynamic contrast enhanced MR parameters, such as Ve, Ktrans, Vp, and IAUC60, increased in patients with SS, which reflected its pathophysiological mechanism of inflammation, edema and increased vascular permeability. Those pathological changes lead to increased perfusion to the gland and probably lead to a reduction of R2* values. In addition, salivary flow might also be one of the factors influencing the parotid R2* values.

The diagnostic role of MR morphological imaging has been well established by multiple previous studies. The typical nodular appearance of parotid gland tissues on MR images intuitively indicates parotid injury. Valesini et al18 reported a sensitivity and specificity of 70.5% and 100%, respectively, with nodular grade by MR imaging in the diagnosis of SS. Takashima et al15 and Makula et al16 suggested that structural MR imaging was not optimal in the diagnosis of SS due to its low sensitivity. In this study, the specificity of the parotid gland nodular grade was 100%, but the sensitivity was only 54.17% in the diagnosis of SS. Meanwhile, the performance of the R2* values of the parotid glands alone in the diagnosis of SS was also not satisfactory: with a cutoff value of 64.14/s, the sensitivity was only 62.5% and the specificity was 100%. Hence, the nodular assessment and R2* value were combined by us for the diagnosis of SS, leading to
positive findings from either modality indicating the existence of SS, whereas negative findings from both modalities excluded the diagnosis of SS. The sensitivity of the combined criteria increased to 87.5%, and the specificity remained 100%. To our knowledge, this is the first attempt to explore the role of parotid T2*/R2* value in quantitative assessment of SS. From the perspective of clinical practice, BOLD MR imaging has a great advantage because it lasts only 37 seconds without any use of extraneous contrast agents, and its post-processing is simple with quantitative outcomes (T2* or R2* values).

There was no significant correlation between the parotid T2*/R2* value and the MR gland nodular grade, which might be due to the small sample size in this study. Similarly, Ding et al. also reported that the ADC values of the parotid glands did not significantly correlate with the nodular grade. There were some limitations to our study. First, the sample size was relatively small to achieve a definite conclusion, but this was still the largest radiologic study of SS to date. Second, 10 TE values with a maximum of 40 ms were arbitrarily selected for BOLD sequence in our study without further optimization of the TE values. As the parotid gland injury aggravated, fat deposition within the gland parenchyma increased, which might impact the T2* measurement of the parotid gland. The MR sequences combined with fat suppression or MR data collected in phase might be helpful to reduce the impact of fat content on the T2* measurement. Third, static T2* and R2* changes did not just reflect changes in BOLD (as with stimulus response and fMRI changes), they also reflected the changes of the loss of normal gland architecture and secretory function, lymphocytic and plasma cell infiltration. Fourth, we did not compare the difference of parotid T2 signal intensity between SS patients and healthy volunteers. Fifth, we took account of only the MR nodular grade for morphological assessment of the parotid glands without evaluation of the parotid ductal system. Sixth, the dilated parotid ducts containing saliva in some patients with SS could inevitably affect the measurement of the mean R2* value. A histogram analysis may solve this problem. Seventh, the salivary flow rate might impact the T2* values. Lastly, the diagnostic performance of other functional MR sequences, such as diffusion weighted imaging and dynamic contrast-enhanced MR imaging, was not evaluated or compared with BOLD MR imaging. All of the above limitations necessitate further research.

CONCLUSIONS

Our study confirmed the feasibility of R2* values for the assessment of the parotid glands in patients with SS, which improved the diagnostic sensitivity especially in normal appearing parotid glands.

REFERENCES


