Radiation-Induced Xerostomia: Objective Evaluation of Salivary Gland Injury Using MR Sialography

BACKGROUND AND PURPOSE: Xerostomia (dry mouth) is one of the serious complications of head and neck irradiation and has a strong influence on a patient’s activities of daily living. MR sialography with salivary secretion stimulation provides additional functional information (salivary secretion reserve) and may contribute to the evaluation of the severity of xerostomia and predict the risk of developing a radiation-induced xerostomia. This aim of the study was to analyze MR sialography as an objective tool to evaluate radiation-induced salivary injury.

MATERIALS AND METHODS: MR sialography with salivary secretion stimulation was performed in 16 patients with head and neck malignancy before and after irradiation therapy. Multivariate (stepwise multiple regression) analysis was performed to analyze the nonstimulated and stimulated MR sialography findings and the clinical severity of xerostomia.

RESULTS: Multivariate analysis of the preirradiation study revealed no significant independent variables that could predict the clinical severity of xerostomia. In the postirradiation study, following regression with 2 independent variables (secretion response of the submandibular gland [rSG] and parotid gland visualization on stimulated MR sialography [sPG]) could explain 70% of the cases: xerostomia severity grade = 0.681 + 0.871 × rSG − 0.471 × sPG.

CONCLUSIONS: MR sialography is a useful method for visualization of salivary gland radiation injury and estimation of the severity of radiation-induced xerostomia. Insufficiency of secretion reserve at the irradiated submandibular gland has the strongest influence on xerostomia severity. Our investigation suggests that careful submandibular gland protection may lead to prevention and avoidance of radiation-induced xerostomia.
posing portal irradiation to the head and neck region. The bilateral parotid and submandibular glands were included in the radiation field; the irradiated dose was 46–64 Gy.

For clinical evaluation of xerostomia severity, we introduced an original grading scale modified from CTCAE, Version 3.0 (Table). In our evaluation, xerostomia severity was classified into 3 grades (grade 1, mild; grade 2, moderate; and grade 3, severe).

Initial MR imaging was performed before treatment, and the postirradiation study was performed within a week after the last irradiation. All MR imaging examinations were performed with a 1.5T superconductive MR imaging unit (Gyroscan ACS-NT; Philips Medical Systems, Best, the Netherlands) with bilateral 14-cm diameter surface coils for the temporomandibular joints. MR sialography was performed with 2D-thick sectioned heavy T2-weighted turbo spin-echo sequences with the following parameters: TR/TE, 10,000/1000 ms; number of averages, 6; turbo spin-echo factor, 6; spectral presaturation with inversion-recovery fat-suppression technique; FOV, 140 × 140 mm; matrix, 512 × 512; separate 27-mm section thickness of each side; and total imaging, 4 minutes 10 seconds. MR sialography was performed before and after salivary secretion stimulation with intraoral administration of the tongue (Fig 1.).

MR sialography grading was performed on each parotid and submandibular gland with both nonstimulated and stimulated status. The morphologic finding of each salivary gland was classified into 3 grades by using the following criteria: grade 1, a distinct depiction of both the main trunk and branches; grade 2, a distinct depiction of the main trunk or first- and second-order branches; grade 3, an indistinct depiction of the main trunk and first- and second-order branches (Fig 2). The salivary secretion function (reserve) was evaluated by comparison of salivary duct visualization at nonstimulated and stimulated MR sialography.

Response to salivary secretion stimulation was classified into 3 grades with the criteria shown in Fig 3. Grade 1 (good response) is a distinct depiction improvement at the main trunk and distal branches, grade 2 (fair response) is a distinct improvement at the main trunk or distal branches, and grade 3 (poor response) is no distinct response at either the main trunk or distal branches (Fig 3).

For MR sialography grading of duct visualization or secretion response, we were concerned that a laterality of grades sometimes occurs. In these situations, a lower (less severely) grade was adopted to avoid an overestimation of salivary gland disturbance.

In our investigation, 3 kinds of grading (nonstimulated [ns], stimulated [s] MR sialography images, and response [r] to stimulation) were obtained from the parotid gland (PG) and submandibular gland (SG). To evaluate the relation with radiation-induced xerostomia, 6 factors obtained from MR sialography (nsPG, nsSG, sPG, sSG, rPG, rSG) were introduced to multivariate analysis by using a stepwise multiple regression method (Stastical Package for the Social Sciences; SPSS, Chicago, Ill). In the analysis, a clinical grade of xerostomia was fixed to a target variable (dependent variable), and 6 factors from MR sialography were defined as explanatory variables (independent variables). In the stepwise method, break criteria for each explanatory variable injection were fixed at ≤5% of the significant level of the partial regression coefficient.

**Clinical grading scale of xerostomia**

| Grade | Characteristics |
|-------|-----------------|
| 1, Mild | Symptomatic (dry or thick saliva) without significant dietary alteration |
| 2, Moderate | Symptomatic and significant oral intake alteration (eg, copious water, other lubricants, diet limited to purees and/or soft moist foods) |
| 3, Severe | Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or parenteral nutrition indicated |

* Clinical severity of radiation-induced xerostomia is classified into 3 grades using CTCAE Version 3.0 modified criteria.

Fig 1. MR sialography findings and response to salivary secretion stimulation. A and B, Oblique-sagittal projection MR sialography of a normal (preirradiated) salivary gland before ([A]) and after ([B]) secretion stimulation. Salivary secretion stimulation with tartaric acid administration on the tongue improves the depiction of the main duct and distal branches.

Fig 2. Morphologic evaluation (grading) criteria of the salivary gland system on MR sialography. On nonstimulated and stimulated MR sialography, each salivary gland (parotid and submandibular gland) is classified into 3 grades according to the degree of lumen visualization: grade 1, a distinct depiction of both the main trunk and branches; grade 2, a distinct depiction of the main trunk or first- and second-order branches; and grade 3, an indistinct depiction of the main trunk and first- and second-order branches.
The results of MR sialography-based grading of pre- and postirradiation parotid and submandibular glands and their salivary secretion responses are shown in Figs 7 and 8. MR sialography findings of initial (nonirradiated) parotid and submandibular glands revealed individual differences in salivary gland visualization and response to salivary secretion stimulation (Fig 7). Multiple regression analysis with the initial (preirradiation) MR sialography findings and clinical xerostomia grade revealed no variables that could predict the clinical severity of radiation-induced xerostomia.

On the other hand, postirradiation MR sialography revealed 2 variables (sPG and rSG) as significant factors that could explain the clinical severity of radiation-induced xerostomia. The following regression equation with a postirradiation MR sialography could explain the clinical severity (grade) of xerostomia: xerostomia grade = 0.681 + 0.871 × rSG − 0.471 × sPG.

A multiple coefficient of determination was calculated at 0.698 (69.8%), and the analysis of variance was significant at the 1% standard. For the absolute value of the standardized partial regression coefficient, rSG (0.984) was superior to sPG (0.486).

Discussion
Salivary glands consist of major (parotid, submandibular, and sublingual) and minor glands. A major salivary gland has a main duct opening to the oral cavity for secreting saliva. Minor salivary glands are widely distributed over intraoral mucosa, and they secrete saliva directly from acini buried in the mucosa. The major function of secreted saliva is as a digestive juice. Other roles include intraoral moistening, antibacterial effect and sanitization, and buffering for prevention of dental caries. The submandibular gland is a serous-dominant mixed gland that continuously secretes saliva (resting saliva secretion). In humans, saliva secretion from submandibular glands accounts for >60% of the total amount of daily saliva secretion, and this resting saliva contributes to intraoral moistening and disinfection.9-11 The parotid gland is a serous gland and secretes digestive enzymes such as amylase for digestion, whereas the sublingual gland is a mucous gland that helps with food softening and mucosal protection.

Radiation-induced xerostomia, a serious complication of radiation therapy for head and neck malignancies, often occurs from the early stage of radiation therapy and strongly affects a patient’s activities of daily living.13 As the radiation exposure dose to the salivary glands increases, the damage progresses and finally becomes irreversible.13 High-dose radiation exposure to the salivary gland increases the incidence of xerostomia and aggravates its severity.14-17 A computer-controlled irradiation technique called intensity-modulated radiation therapy (IMRT) has been introduced to reduce the radiation exposure of salivary glands and minimize radiation exposure to surrounding normal tissues. Eisbruch et al17 reported the utility of IMRT to avoid parotid gland impairment and to contribute to the prevention of xerostomia. However, several reports reviewed the relationship between the exposure dose of parotid and submandibular glands and the severity of radiation-induced xerostomia,19-20 and it was found that serious xerostomia easily occurred after a larger exposure dose to the submandibular gland. These reports postulated
that the xerostomia severity was related to submandibular gland injury. The authors found that poor intraoral moistening lead to the onset of xerostomia, and they reported that when resting saliva secretion dropped to half of its baseline volume, patients experienced xerostomia.9

Seikaly et al21 and Al-Qahtani et al22 reported that the preliminary surgical transplantation of submandibular glands contributed to the prevention of radiation-induced xerostomia. The fact that most resting saliva is supplied from the submandibular gland supports the relationship between submandibular gland hypofunction and xerostomia. Our investigation results also support the relationship between submandibular gland hypofunction and the severity of radiation-induced xerostomia.

In our regression equation, another factor that explained xerostomia severity was sPG. Moreover, the coefficient showed a negative number ($-0.471$). In 3 of our 16 patients, the negative coefficient of sPG compensated for a grading er-

Fig 4. MR sialography (inverted images) before (A and B) and after (C and D) 46-Gy irradiation to the salivary gland. (A and C, nonstimulated; B and D, stimulated images). Initial (preirradiation) MR sialography of the right salivary system shows good depiction of parotid and submandibular gland ducts and response to secretion stimulation (A and B). Irradiation to the salivary gland induces insufficient visualization of the main trunk and distal branches and disturbs salivary secretion response (C and D).

Fig 5. Nonstimulated (A) and stimulated (B) MR sialography of mild radiation-induced xerostomia. Images show nonstimulated (A) and stimulated (B) MR sialography of the 62-Gy irradiated right salivary system. Both parotid and submandibular glands show good depiction of the salivary duct and secretion response. The clinical xerostomia grade and MR sialography grade for this patient are 1 and 1.08.
ror (overestimation) induced by a high grade of rSG (Fig 9). The negative number coefficient of sPG seemed to contribute to compensation for the grading error that came from individual differences of salivation function.

In our investigation, preirradiation MR sialography with secretion stimulation could not help predict the severity of radiation-induced xerostomia. Regression equations obtained from postirradiated MR sialography revealed that submandibular gland secretion response is the most influential to radiation-induced xerostomia grading. Our results mean that hypofunction of the irradiated submandibular gland has the strongest influence on the clinical severity of xerostomia. In radiation therapy for head and neck malignancies, protection of the submandibular glands from excessive radiation exposure is suggested to be important for the prevention of radiation-induced xerostomia. To protect the submandibular glands from excessive irradiation, development of new irradiation techniques and new specific protection drugs are expected.

Conclusions
MR sialography with secretion stimulation can be a valuable tool to evaluate radiation-induced salivary gland disturbance. Hyposfunction of the irradiated submandibular gland has the strongest influence on the clinical severity of xerostomia. For prevention of radiation-induced xerostomia, protection of the submandibular gland from excessive irradiation is highly important.

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