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Using Gene Transfer Technology to Restore the Salivary Gland Function in Xerostomia Patients following Radiation Therapy of Head and Neck Cancer

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Abstract

Many diseases can be treated by gene therapy using a modified virus to carry the corrected required gene to infect the target cells. The goal of this report is presenting the planning for gene therapy for patients suffering from head and neck cancer to alleviate their loss of saliva function.

Keywords: Head and Neck Cancer; Gene Therapy; Saliva; Salivary Gland

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Introduction

Radiation therapy plays an important role as one of the best methods used in treating head and neck cancer [1]. It can be used as a sole treatment method in the early stages of cancer, but it is also used in combination with other treatments, such as surgery and chemotherapy in more advanced cases [2,3]. In very advanced cases that have lost the chance of treatment, radiotherapy is also applied as a palliative measure to reduce the mass, reduce pain, stop bleeding, and reduce pressure on other structures [4,5]. However, radiotherapy can also cause major side effects. Both the neck and head are affected by radiation therapy, and disturbances in the functions of the neck and head are considered side effects resulting from radiation [6,7]. Acute side effects of radiotherapy applied in the treatment of head and neck cancers suggest secondary cell death, which is caused by the combination of intracellular free radical production and ionizing radiation, and actual organelle damage or inadequate repair of deoxyribonucleic acid (DNA) damage in dividing cells [8–12]. Mucositis, second-degree skin burns, wet desquamation, all salivary function losses, fibrosis in the skin and underlying tissues of the applied area, loss of taste, nutritional problems, edema in the face and neck, hair loss, dental problems are mostly acute effects of radiation on cellular systems with rapid turnover cycles [13–16]. Chronic side effects include muscle fibrosis, skin atrophy, brain necrosis, neuropathy, esophageal stricture, retinopathy, cataract formation, and radiation myelitis. These are either the direct effects of radiotherapy or the microvascular tissue insufficiency caused by endothelial proliferation and fibrosis resulting from radiotherapy.

Subjects and Methods

General Plan and Patient Selection

A randomized prospective study was planned to compare the effects of drugs containing amifostine and zinc sulfate to prevent dry mouth (xerostomia) that occurs after treatment in patients receiving head and neck radiotherapy [17,18].

Eligible patients include those who will receive only radiotherapy or

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chemoradiotherapy for treatment purposes, those who were diagnosed with head and neck cancer or those who had previously received radiotherapy or chemotherapy, and those diagnosed with head and neck cancer that previously received radiotherapy or chemotherapy. All cases were over 15 years of age and under 80 years old.

The patients were evaluated by two different physicians working in the radiation oncology clinic before treatment, every week during treatment, and two months after the end of treatment, and that included oropharyngeal examinations, routine blood tests, and weight assessments.

Mucositis assessments were made based on the Radiation Therapy Oncology Group (RTOG) oropharyngeal mucositis classification system. The date of onset and degree of mucositis were recorded. In addition, to clinically evaluate the saliva volume of each patient, saliva volume was measured before treatment, at the end of treatment, and in the second month after treatment. For this purpose, the patient was asked to rinse his/her mouth thoroughly with water and spit before each measurement. Then, he/she was asked to spit all the saliva accumulated in his/her mouth into a 10 mm diameter glass tube.

After the procedure was completed, he/she waited for 5 minutes. Freshly squeezed lemon juice (citric acid) was used to measure the amount of stimulated saliva. 3 ml of lemon juice was dropped onto the back of the tongue using a tongue depressor, and the patient was asked to gargle the lemon juice in his/her mouth for one minute. At the end of the period, the patient was asked to spit out the lemon juice and then spit the saliva that had accumulated in his/her mouth into a second glass tube as described above. The saliva obtained was measured and recorded in millimeters from the outer surface of the glass tube.

The Outpatient Department in our Maxillofacial and Research Centre at UAE treated five patients who have complained of post operative radiation (as a side effect). Most of those patients complained of dry mouth (xerostomia). Two male patients over 50 years, one patient of 60 years, one male patient was 75 years old, and only one female patient aged 70 years old were treated.

Radiotherapy

Radiotherapy was applied with a multifiber collimator linear accelerator (LINAC MLC, Siemens) device in 1.8-2 Gy dose fractions 5 days a week for 5-7 weeks.

Before starting radiotherapy, immobilization was provided with a thermoplastic mask in all patients, lead markers were placed at certain points and tomography was taken for planning purposes, and the images obtained were transferred to our clinic's 3D planning system. The most appropriate radiotherapy areas for each patient were planned based on these images.

Patients were treated with the conformal radiotherapy technique suitable for the planned radiotherapy area. During radiotherapy, radiotherapy was and/or the decision to suspend chemotherapy was made independently by two physicians working in the Radiation Oncology Clinic.

Examination of Salivary Glands by Scintigraphic Method [19,20] ***(Figure 1)***

A total of three salivary gland scintigraphy scans were planned for all patients, before radiotherapy, at the end of radiotherapy, and two months after radiotherapy. However, some of the patients did not accept salivary gland scintigraphy scans at the end of radiotherapy due to oral mucositis or other reasons. Therefore, it was decided to evaluate all patients based on the scintigraphic images taken before radiotherapy and in the second month after radiotherapy.

A parallel-hole, low-energy, high-resolution collimator was selected in the study and a single-head gamma camera. The energy level was determined to be 140 keV and the windows interval as 20%.

The patients were positioned in a supine position under the gamma

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camera detector, with the head slightly extended. Following the given intravenously of 185 MBq (5mCi) technetium 99m- pertechnetates as a bolus, 25 images, each lasting 60 seconds, were obtained. Dynamic images were obtained for 25 minutes, with a matrix of 128x128 and a zoom of 1.33. Three milliliters of concentrated lemon juice was administered into the oral cavity via an injector at 20 minutes. A total of 25 images were taken during the dynamic study.

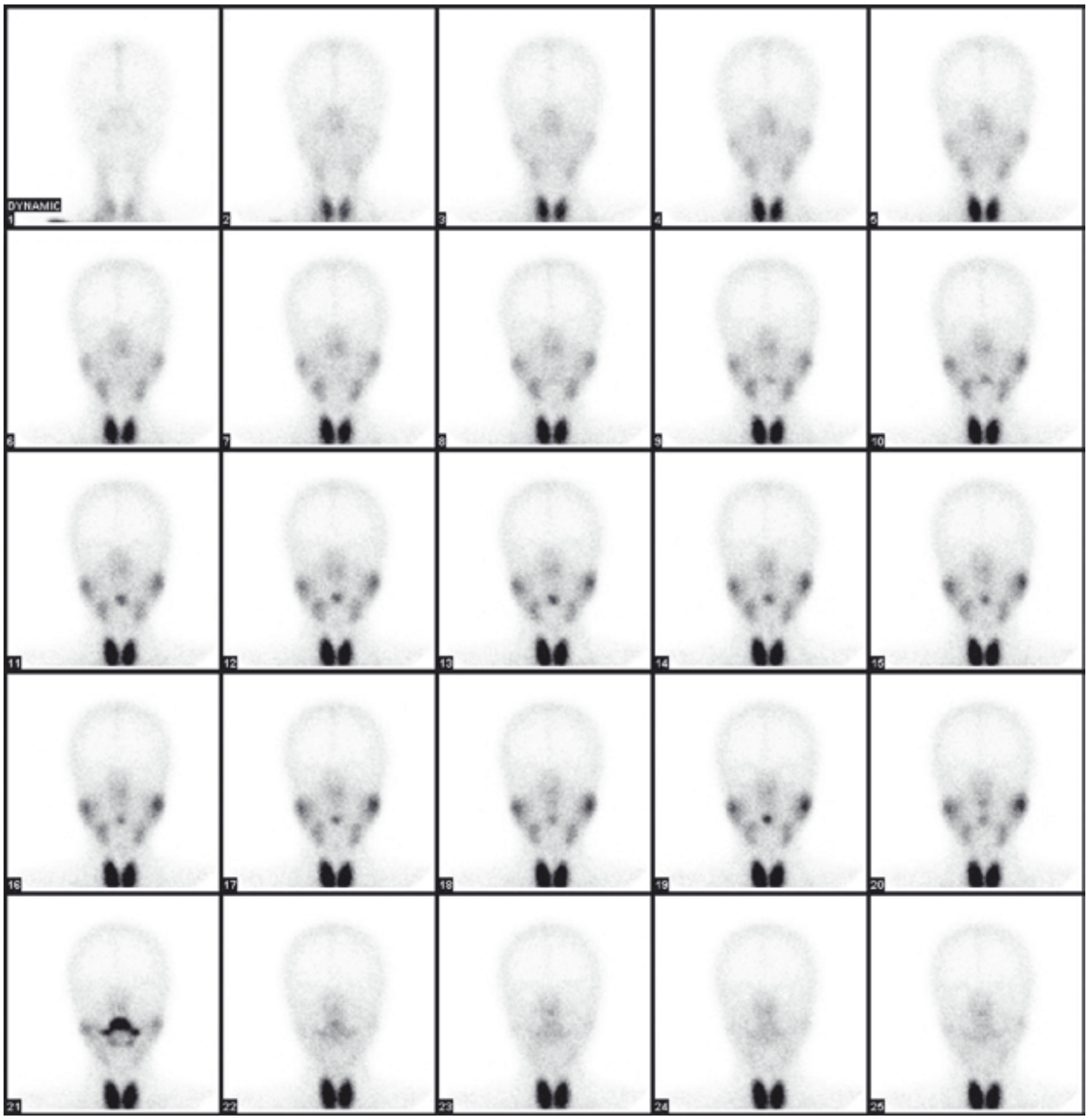

Figure 1. *Dynamic images of salivary gland scintigraphy.*

In the collected images, regions of interest were drawn around the right and left parotid glands, right and left submandibular glands for semiquantitative analysis. Similarly, a region of interest was drawn in the temporal region for background activity (Figure 2).

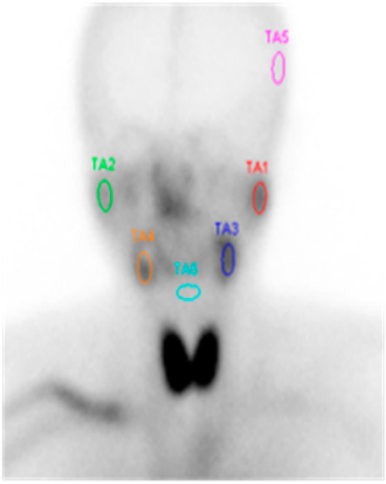

Figure 2. *Determining areas of interest for each salivary gland.*

Results and Conclusion

Five patients (Table 1) were admitted to our Maxillofacial and Research Center with a history of radiation therapy to the parotid gland or areas in the head and neck due to maligned tumor, with the main complaint xerostomia (dry mouth). The patients are unable to eat or talk normally. These patients were treated in our Maxillofacial and Research Center by gene therapy.

Aquaporin gene therapy restored the diminished saliva in the treated patients.

Gene therapy for restoration the function of the salivary gland gave a satisfactory result in two patients, with no complications reported.

These two patients died within two years after the treatment (gene therapy) due to metastasis of the malignant tumors; the period of the follow up been very short.

Table 1. *Patients treated by gene therapy.*

Gender	**Results of patients treated by gene therapy**
Male	2 Patients Complete Failure
Female	1 Patient Unsatisfactory Result
Male	2 Patients Satisfactory Result

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

All the authors declare no commercial or financial conflict of interest.

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