TASTE DYSFUNCTION IN PATIENTS RECEIVING RADIOTHERAPY

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Abstract: Background. Taste loss is a major cause of morbidity in patients undergoing head and neck irradiation.

Methods. In a prospective study, 51 patients undergoing radical head and neck irradiation at the Tokyo University Hospital were assessed for taste loss. Taste ability was measured by the taste threshold for the four basic tastes (sweet, sour, salt, and bitter qualities) plus another taste of “umami” quality using a filter-paper-disc method in patients before, during, and after radiotherapy (RT).

Results. All tastes declined on the fifth week after the start of RT and improved on the 11th week. Anatomic pathologic analyses in rats revealed that taste buds diminished completely on the sixth day after irradiation of 15 Gy in a single fraction, and the appearance of taste buds returned almost to the preirradiation state on the 28th day.

Conclusions. The main cause of taste disorder resulting from RT was believed to be a disappearance of taste buds and not damage to the taste nerves.

Keywords: radiotherapy; taste dysfunction; taste bud; filter-paper-disc; taste changes; head and neck cancer

One of the most frequent complaints of patients undergoing radiation therapy (RT) for head and neck cancer is taste dysfunction. Complaints of taste disorders have been reported in 75% of patients with head and neck cancer undergoing radiation, and 93% of these patients complain of long-term xerostomia. Many patients undergoing dose-intensive radiation experience reduced taste (ageusia) or altered taste (dysgeusia), which may have a significant impact on quality of life. It has been reported that the causes of taste disorders are a combination of various factors. These include: (1) the disappearance of taste buds; and (2) dysfunction of the salivary glands, leading to the inability of taste substances to penetrate the taste pores, as well as direct damage to the taste receptors and/or to the nervous system, which transmits signals to the gustatory area in the brain. However, a definitive understanding of the mechanism of these taste disorders remains obscure.

The relationship between changes in the taste recognition threshold in the four basic tastes plus one new taste “umami (amino acid)” (the taste of monosodium glutamate) and the timing of radiation were analyzed. In addition, we compared the outcomes with microscopic morphologic changes of the rat tongue after a single high-dose radiation.
PATIENTS AND METHODS (HUMAN STUDY)

The subjects were 51 patients who underwent RT for their head and neck cancers at the Tokyo University Hospital from May 1999 to January 2004. Nine of the subjects had nasopharyngeal cancer, 20 had oropharyngeal cancer, two had both oropharyngeal and hypopharyngeal cancer, 16 had hypopharyngeal cancer, and four had other cancers. The mean age was 64 years (range, 29–89 years). There were 44 men and seven women. Most patients were in good general condition (the rate of Karnofsky performance status ≥90% was 78%). In most patients, the RT was administered as a dose of 1.8 Gy once a day, five times each week. The total RT period ranged from 8 to 12 weeks. The radiation technique in this study was conventional radiation. Photon energy only was used. We performed off-cord reductions at 43.2 Gy in 24 fractions. The anterior oral tongue was deflected from the radiation volume after off-cord. Concurrent chemotherapy was allowed in this study. Forty subjects (78%) underwent chemotherapy combined with RT.

The cancers were limited to the head and neck area. Patients who had only a part of tongue within the radiation field were excluded from the study.

LINAC (6 MV in most cases) was used as a radiation source. In most cases, from start to 43.2 Gy in 24 fractions, the radiation method was three fields (their gantry angles were 0, 80, and 280 degree and beam weight was 1:1:1) (Figure 1). The nasopharynx radiation treatment also included the oral tongue within the volume of tissue radiated. After that, up to 59.4 Gy in 33 fractions, we used two shrinking and right-opposing and left-opposing fields. In addition after that, the radiation field to the tumor bed was reduced. Most patients received a total radiation dose of 72 Gy in 40 fractions. The determination of the radiation fields was confirmed with LINAC-graphy.

No tumor ablative procedures, altering salivary beds, were performed in this study. No patients were taking Salagen or amifostine. None of the enrolled subjects had total or partial glossectomies.

All subjects gave written informed consent before entry into the study. The subjects had no intercurrent illnesses that affected salivary function (ie, Sjögren's syndrome, human immunodeficiency virus [HIV]). No concurrent medicines altering the taste of the subjects were administered.

The filter-paper-disc method (using taste-disc: Sanwa Kagaku Kenkyusho Co., Ltd, Nagoya, Japan) was used to measure thresholds of four basic tastes under each gustatory innervation.

For the four basic tastes, purified sucrose was used for sweet, sodium chloride was used for salty, tartaric acid was used for sour, and quinine hydrochloride was used for bitter. Each basic taste test solution was prepared with distilled water, and the tests were performed at room temperature. The taste concentrations of the test solutions were arranged in five concentration levels (1–5) for each taste and are shown in Table 1.

The taste testing procedure was as follows:

1. The subject was asked to place the taste indicator chart (Table 2) in front of him.
2. While a filter paper disc was held with tweezers, the most dilute sweet solution was dropped onto the disc to moisten it. Testing started with the sweet taste.
3. The moistened disc was gently placed on the specified part of taste measurement.
4. The subject was asked to select the corresponding taste from the indicator chart within a few seconds, with his mouth open.
5. The filter paper disc was removed with tweezers.
6. If a correct answer was not given, the same procedure was repeated with the remaining test concentrations, increasing to more concentrated solutions until a recognition threshold was determined.
7. To avoid the residual effects of the previous test solution, the subject rinsed adequately with water, and an interval of more than 1 minute...
8. The same manipulations were used, and the tests proceeded successively to salty, sour, and bitter, and their recognition thresholds were determined. Before switching taste test solutions, the subjects rinsed their mouths with a cup of distilled water.

9. Bitter was the last taste tested, and the same procedure for recognition threshold was used.

For 13 patients, who had been started on the taste testing procedures since April 2002, an additional taste of “umami” was added after the bitter test. The taste recognition threshold for “umami” was measured using the whole-mouth taste method. Test solutions of monosodium glutamate (MSG; 25, 50, 75, or 100 mM) were prepared, and the subjects were tested with 10 mL of each concentration for a recognition threshold.

These taste recognition threshold measurements were performed once before RT and performed weekly from the first week to 10 to 12 weeks after the start of RT. At the same time, the radiology oncologists asked the subjects about xerostomia from RT.

The filter paper disc was 5 mm in diameter. In conducting the test, the disc was placed on the anterior part of the tongue (Figure 2). Subjects were asked to extend the tongue as far as possible as put on the proximal edge of the extended tongue.

In determination of test results, sensibility of taste was scored as “5” when the subject recognized the No. 1 concentration (see Table 1) of each taste solution, as “4” for the No. 2 concentration, as “3” for the No. 3 concentration, as “2” for the No. 4 concentration, and as “1” for the No. 5 concentration. When the No. 5 test concentration was not recognized, the score was “0.”

RESULTS (HUMAN STUDY)

Patients. The mean and median total doses of RT for tip of the tongue were 13.7 Gy and 13.3 Gy (range, 11.4–15.2 Gy) and for the posterior part of the tongue were 65.3 Gy and 70 Gy (range, 38–80 Gy).

Salivary function of the subjects was normal in pretreatment, but most subjects never or hardly secrete saliva on and after the third week after the start of RT.

Taste Recognition. Changes in the taste recognition threshold for each taste every week during and after RT are shown in Figure 3. Analysis with the F test showed a significant difference only between salty and sweet ($p = .0209$), salty and bitter ($p < .0001$), and salty and sour ($p = .0010$). In addition,

## Table 1. Composition and description of test solutions.

<table>
<thead>
<tr>
<th>Test solution</th>
<th>Concentration 1</th>
<th>Concentration 2</th>
<th>Concentration 3</th>
<th>Concentration 4</th>
<th>Concentration 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified sucrose</td>
<td>8.8 mM</td>
<td>73 mM</td>
<td>0.29 M</td>
<td>0.59 M</td>
<td>2.3 M</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>52 mM</td>
<td>0.22 M</td>
<td>0.86 M</td>
<td>1.7 M</td>
<td>3.4 M</td>
</tr>
<tr>
<td>Tartaric acid</td>
<td>1.3 mM</td>
<td>13 mM</td>
<td>0.13 M</td>
<td>0.27 M</td>
<td>5.3 M</td>
</tr>
<tr>
<td>Quinine hydrochloride</td>
<td>0.25 mM</td>
<td>0.5 mM</td>
<td>2.5 mM</td>
<td>13 mM</td>
<td>0.1 M</td>
</tr>
</tbody>
</table>

## Table 2. Indication chart for taste.

- Sweet
- Salty
- Sour
- Bitter
- Unusual taste
- No taste

FIGURE 2. Photograph demonstrates the site where a taste disc was placed. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
Table 3 shows the mean taste test results and p value of each taste test immediately before the start of RT and at the fifth and eleventh weeks after the start of RT. The paired t test was used in calculating these values. The significance level was set up as .05. Figure 4 shows changes in the taste recognition threshold for “umami” every week during and after RT. For all four basic tastes and “umami,” the sensitivity of taste declined significantly between the start of testing and the fifth week after beginning RT (at 45 Gy). For all four basic tastes, except “umami” on the 11th week after the start of RT, the sensitivity of taste improved significantly compared with the fifth week.

The data analyzed for those who had concurrent chemoradiation therapy versus radiation alone are shown in Figure 5. The F test was performed between two groups, those with and those without chemotherapy; the F value was 1.037 and p value was .6099. Consequently, the effect with and without chemotherapy did not differ.

MATERIALS AND METHODS (ANIMAL STUDY)
In another series of experiments, rats were irradiated with 15 Gy in a single fraction with 6 MV to determine the number of days after irradiation for the detection of microscopic morphologic changes of the circumvallate papillae. Figure 6 shows a plain x-ray film for checking the radiation field that was 3 cm × 3 cm.

After the rats were killed on days 4, 6, 8, 13, 23, and 28 after irradiation, the surfaces of the tongues were stained with hematoxylin and eosin (H & E).

To see the changes in nerve distribution between preirradiation and the eighth day after irradiation of 15 Gy, we performed antibody staining with avidin-biotin complex (ABC) method using monoclonal antibody for neuron filament, 2H3. After a positive signal was detected using 3,3`-diamoniobenzidine (DAB) as a substrate, H & E staining was done.

RESULTS (ANIMAL STUDY)
The morphologic changes of circumvallate papillae after irradiation of 15 Gy are shown in Figure 7. Pathologic analyses revealed that on the fourth day after irradiation (Figure 7B), there was a decline in the number of taste buds and the appearance of papilla began to change. On
the sixth day (Figure 7C), the epithelium of circumvallate papillae became very thin, and taste buds diminished almost completely. On the eighth day (Figure 7D), the epithelium of circumvallate papillae became very thick again, but taste buds were still diminished. On the 18th day (Figure 7F), taste buds started to re-emerge here and there. On the 23rd day (Figure 7G), a part of and a small number of taste buds showed a recovery to their former appearance. On the 28th day (Figure 7H), an increase in the number of taste buds was noted, and their appearance returned almost to the preirradiation state. Figure 8 shows the relationship between the number of taste-bud cells and the days after irradiation. The number of taste-bud cells diminished almost completely by 6 days after irradiation and returned to about 80% on the 19th day. However, changes in nerve distribution were not seen between preirradiation and on the eighth day after irradiation of 15 Gy (Figure 9).

DISCUSSION

About Our Human Results. The taste disc method used in this study can measure taste disorders with respect to four basic tastes (sweet, salty, sour, and bitter) semiquantitatively and has no effect on other sensations of the somatic sensory system. The filter-paper-disc method can detect taste disorders as sensitively as electrogustometric (EGM) measurements.4

The reason for the deterioration of the sweet, sour, salt, and bitter taste sensitivities reaching a peak on the fifth week after the start of RT was thought to be a large RT field, which contained the anterior part of the tongue, and which was completed on the fourth week (at 43.2 Gy in 24 fractions).

In an original article written in 1894, Kiesow5 revealed that sweet was more sensitive in the apex of the tongue than in any other site, sour in the margin of the tongue, and bitter in the base of the tongue. However, in 1994, Kitagoh and Tomita6 concluded that there was no basis to support the existence of the so-called tongue map, that is, there was no difference in taste sensitivity at the part of tongue.6

Cancer and its treatment cause malnutrition in 40% or more of hospitalized patients.7 Malnutrition is associated with poor prognosis, decreased response to therapy, prolonged/enhanced morbidity of therapeutic side effects, and decreased quality of life. In one study, 45% of hospitalized adult patients lost 10% of their body weight, whereas 25% lost 20% or more of their body weight.7 Taste disorders contribute to malnutrition in patients with cancer.

Unfortunately, taste disorders in the oncology setting have been understudied and, indeed, are likely to be underestimated, making recommendations concerning diagnosis, therapy, and prognosis of taste dysfunction difficult. Data published on taste changes in patients undergoing RT are very limited.

Other effects on taste dysfunction of RT may result from damage to receptors; patients affected in this way often complain of a metallic taste. Such effects may take more than 6 months to resolve.1,8,9 During a course of curative RT for head and neck cancer (eg, 60–70 Gy given over 6–8 weeks), salivary function was observed to
FIGURE 7. Morphologic changes in epithelium of the circumvallate papillae after irradiation with 15 Gy (hematoxylin-eosin stain). Pre-irradiation (A), and on the fourth (B), sixth (C), eighth (D), 13th (E), 18th (F), 23rd (G), and 28th (H) day after irradiation. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
decrease by the end of the first week, and taste function was measurably impaired by the end of the second week of treatment.\textsuperscript{1} The maximum tolerance doses resulting in a 50\% complication rate 5 years after treatment (TD 50/5) were estimated to be 40 to 65 Gy for xerostomia and 50 to 65 Gy for taste loss.\textsuperscript{1} Initial assessment of patients’ reports of taste changes during RT has shown that there is considerable change during treatment and that pretreatment taste sensation is not recovered.\textsuperscript{10–12} These taste complications may be due to direct effects on taste receptors and to reduced saliva production, resulting in secondary infection and reduced delivery of taste substances to receptor sites.

Antineoplastic drugs that have been associated with taste changes include cisplatin, carboplatin, cyclophosphamide, doxorubicin, 5-fluorouracil, levamisole, and methotrexate.\textsuperscript{13} But in this study, as shown in Figure 9, antineoplastic drugs had no or little effect on these patients. Xerostomia, which can be due to RT, may be responsible for taste changes. Damage to salivary glands may reduce the flow of saliva to such an extent that taste substances are not diluted and do not reach the receptor, which may result in food that is tasteless.\textsuperscript{13} Changes in the oral flora, with overgrowth of fungi, some bacterial species, and increased dental caries may also lead to altered taste.\textsuperscript{12}

Mossman and Henkin\textsuperscript{14} studied a group of eight patients with head and neck cancer receiving radiation over a period of 7 weeks. Increased threshold values were noted for all taste modalities after 3 weeks of RT. They reported increased sour thresholds with a mean of 500 mmol/L. Four of the eight patients in their study showed increased sweet thresholds after treatment, with values ranging from 30 mmol/L to the inability to recognize a saturated solution. They showed a continually increasing threshold for bitter (up to 800 mmol/L) during 7 weeks of RT.

In 1978, Bartoshuk\textsuperscript{15} recorded data on one patient who received a 6-week course of irradiation for cancer of the neck. She reported that the functions of taste intensity performance for all of the four basic tastes decreased 26 days after the

![Image](Grace.png)
start of RT, and the functions were still impaired even after 173 days. Mossman and Henkin tested the threshold and suprathreshold taste performance of eight patients with head and neck cancer. In the suprathreshold test, the taste intensity performance decreased significantly 5 weeks after the completion of RT. The notion that some taste buds functioned in an abnormal manner during and after RT was considered. In 1993, Schwartz et al examined the suprathreshold taste performance of 15 patients who had completed their RT from 6 months to 19 years earlier. The postradiation taste intensity performance of the patients was not significantly different from that of the normal controls. Thus, it is still controversial whether the function of taste intensity performance remains decreased after the completion of RT.

Mossman analyzed the dose-response curve for human taste loss during irradiation by adopting a four-parameter logistic equation and using a nonlinear least-squares fit. He proposed a sigmoid curve model for taste loss, with taste loss increasing rapidly between radiation doses of 10 and 40 Gy, and then increasing slowly from 40 Gy to 60 Gy. However, the actual experimental data showed that the maximum taste loss was observed at 50 Gy and decreased after 50 Gy. His explanation for this decrease was the variability associated with taste loss measurements late in therapy.

We assumed the reason why the number of taste cells decreased apparently after 19 days (Figure 3) was the taste-bud cells once recovered excessively (transient super recovery) and, after that, were given a natural selection and returned to the steady state, although the exact reason remains to be seen.

**About Our Rat Results.** The second part of the study describes the histologic changes in the rat circumvallate papillae. Research studies on the murine taste buds in the past have conclusively proved that changes do, in fact, take place in the taste buds. In studies described previously, they observed the histologic changes of nerve fibers and taste cells in rats at various time points after RT. We also studied the rat lingual papillae.

The time course of gross histologic change in irradiated taste buds and lingual epithelium was essentially in agreement with previous studies on murine fungiform papilla and murine ventral lingual epithelium, respectively.

The effects of irradiation on the taste system were examined in rats given a single dose of 17 Gy irradiation to their oral cavity. The taste nerve fibers were labeled with calcitonin gene-related peptide (CGRP), and the taste cells, especially their membranes, were labeled with neural cell adhesion molecule (NCAM). After the radiation, the distribution of the nerve fibers labeled with CGRP did not change. However, a decrease of NCAM immunofluorescence in taste cells was seen at day 7, but returned to the preirradiation levels at day 11. These data are consistent with the hypothesis that taste loss is caused by damage to the taste cells but not by an impairment of the taste nerve fibers. Shatzman and Mossman studied the effects of irradiation on preparations of enriched bovine taste bud membranes by using differential and sucrose gradient centrifugation. They found that a radiation dose of 70 Gy reduced the protein content in the membrane-enriched fraction. However, radiation seemed to have no effect on the amount of cyclic adenosine monophosphate (AMP), which is bound to the membrane and acts as a second messenger. These results suggest that radiation may cause a structural change in the membranes of the taste buds, but the membranes remain normal with respect to function, which is consistent with the suprathreshold taste performance results in this study. If the taste cell membranes and nerve fibers function normally after irradiation, the function of taste intensity–concentration curves should not change significantly.

Esses et al studied the effects of fractionated radiation on the number of taste buds in mice (five times per week; 1.7 Gy per fraction). The number of taste buds decreased to the minimum (22% of the control animals) at 25.5 Gy (irradiation period, 3 weeks), and after that, it increased despite continued irradiation. At a dose of 42.5 Gy (irradiation period, 5 weeks), the taste bud number returned to 67% of that seen in the control animals. It remains to be solved whether taste bud number and function can recover toward the end of RT.

**Rat Results Help Us Understand What Is Happening in Humans.** Some reports say that basic construction and function are same in mammals. Zhao et al stated that there were no differences in sweet, umami, and bitter receptors among mammalians. Adler et al Matsunami et al and Lindemann reported that there were no differences in bitter receptors between humans and mice. Kullaa-Mikkonen et al said that the
structure of filiform papillae of the rat tongue resembled that of the human tongue.

When the paper-filter-disc method was used on human subjects, the sensitivity of taste started to decline in the early weeks after the start of RT and improvement occurred during the latter part of radiation if the entire tongue was not included in the field. These outcomes coincide with those of pathomorphologic changes in rats, although a single fraction of 15 Gy in the rat could not be thought of in the same way as fractionated radiation in the human.

CONCLUSION

Our data suggest that the taste disorders induced by radiation are mainly caused by damage to the taste buds in the radiation field, and the pattern of the taste disorder is heavily influenced by the distribution of the taste buds damaged during the RT. Much more research is needed to develop an understanding of the nature, frequency, severity, and duration of taste alterations incurred by patients with head and neck cancer undergoing RT.

REFERENCES