

The Long-term Recovery of Parotid Glands and Oral QOL in Nasopharyngeal Cancer Treated by Intensity-modulated Radiotherapy

Shun Tasaka

Department of Radiation Oncology, Tohoku University Graduate School of Medicine

Keiichi Jingu (✉ kjingu-jr@rad.med.tohoku.ac.jp)

Department of Radiation Oncology, Tohoku University Graduate School of Medicine 1-1 Seiryō-chō,
Aoba-ku, Sendai 980-8574, Japan <https://orcid.org/0000-0002-7032-1577>

Noriyoshi Takahashi

Department of Radiation Oncology, Tohoku University Graduate School of Medicine

Haruo Matsushita

Department of Radiation Oncology, Tohoku University Graduate School of Medicine

Rei Umezawa

Department of Radiation Oncology, Tohoku University Graduate School of Medicine

Takaya Yamamoto

Department of Radiation Oncology, Tohoku University Graduate School of Medicine

Yojiro Ishikawa

Department of Radiation Oncology, Tohoku University Graduate School of Medicine

kazuya Takeda

Department of Radiation Oncology, Tohoku University Graduate School of Medicine

Yu Suzuki

Department of Radiation Oncology, Tohoku University Graduate School of Medicine

Noriyuki Kadoya

Department of Radiation Oncology, Tohoku University Graduate School of Medicine

Research

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Abstract

Background

Xerostomia is one of the most common adverse events of radiotherapy in head and neck cancer patients. The purpose of this study was to evaluate longitudinal volume the change of parotid gland after radiotherapy for nasopharyngeal cancer and the relationship between parotid irradiation dose and xerostomia symptoms.

Methods

We retrospectively analyzed longitudinal changing of parotid gland volumes in 20 patients treated by intensity-modulated radiotherapy (IMRT). We assessed xerostomia 4 years or more after IMRT by measuring the degree of oral moisture and oral QOL evaluation.

Results

The relative parotid volumes at 0-6, 7-18, 19-30, 31-42, 43-54 and 55-66 months after IMRT were $67.9 \pm 10.1\%$, $67.7 \pm 13.6\%$, $74.3 \pm 12.5\%$, $75.8 \pm 12.4\%$, $78.3 \pm 17.4\%$, and $75.3\% \pm 17.7\%$, respectively. The parotid volume had recovered significantly at 31-42 months after IMRT, especially in parotid receiving less than 40 Gy. The mean irradiated dose for bilateral parotids showed negative correlations with oral QOL score and oral moisture.

Conclusion

The mean irradiated dose for the parotid should be reduce as much as possible to improve oral QOL long after IMRT.

Background

Xerostomia is one of the most common adverse events of radiotherapy in head and neck cancer patients [1]. Salivary glands are highly sensitive to radiation and they can be damaged by radiation, leading to xerostomia, which causes a decrease in patients' quality of life after radiotherapy [2]. The mechanism of radiation-induced damage of salivary glands, which has been mainly studied in animal models, is thought to be selective damage of the plasma membrane of secretory cells immediately after radiation exposure, followed by damage of DNA, death of acinar progenitor cells and finally lysis of acinar cells [3–7]. Saliva production is reduced after delivery of 10–15 Gy to the parotid gland [8, 9] and although recovery of parotid gland function is possible with the lapse of time after irradiation with 40–50 Gy, higher doses cause irreversible and permanent xerostomia [10–13]. To spare parotid gland function, the recommended mean irradiated dose for the parotid gland is less than 25–30 Gy, and it was reported that saliva production recovers to the same level as that before treatment [14, 15]. Hey et al. observed saliva flow for 36 months after radiation therapy in patients with head and neck cancer and reported that most of the recovery processes were considered complete within that period [16]. In a multicenter randomized

study (PASSRORT trial), the clinical outcomes of intensity-modulated radiotherapy (IMRT) and 3D-comformal radiotherapy (3D-CRT) in terms of parotid sparing were investigated. It was shown in that study that 39% of the IMRT patients and 74% of the 3D-CRT patients suffered from xerostomia at 12 months after treatment [11]. There have been many reports on functional changes of the parotid gland after radiation therapy, but there have been few reports on the volume of the parotid gland and its relationship with oral quality of life (QOL) and even fewer reports on longitudinal change of the parotid gland volume. The purposes of this study were to evaluate the longitudinal volume change of the parotid gland after definitive IMRT in patients with nasopharyngeal cancer and to investigate the relationships among irradiated dose for the parotid gland, parotid gland volume and xerostomia symptoms.

Methods

This research was carried out in compliance with the content of the Declaration of Helsinki, and it was approved by institutional review board in our institution.

Patients selection

We retrospectively analyzed patients with nasopharyngeal cancer who were treated by definitive IMRT combined with chemotherapy in our hospital between 2009 and 2014. Eligibility criteria were as follows: (a) pathologically proven nasopharyngeal carcinoma, (b) longitudinally and regularly evaluation by computed tomography (CT) in our hospital and availability of longitudinal data for 3 years or more, (c) no previously surgery for the head and neck area, (d) no history of diseases causing a salivary secretion disorder such as Sjogren's syndrome, (e) treatment by definitive chemoradiotherapy, and (f) treatment by IMRT.

Radiotherapy

All patients received irradiation to bilateral prophylactic cervical lymph node regions in addition to the primary tumor and region of lymph node metastasis by IMRT. Clinical target volume (CTV) 1 was defined as the primary tumor and region of lymph node metastasis with an appropriate margin, and CTV 2 was assigned to bilateral prophylactic cervical lymph node regions. Planning target volume (PTV) was set with a margin of 5 mm to the CTV. PTV 1 was irradiated with 70 Gy in 35 fractions (fr.) and PTV 2 was irradiated with 40–50 Gy in 20–25 fr. using a 6–15 MV X-ray linear accelerator. Re-planning was conducted in the third or fourth week of IMRT for all patients.

Parotid gland volumes

Longitudinal head-and-neck CT data were transferred to a 3D-radiation therapy planning system (Eclipse, Varian Medical System Inc.) using the digital imaging and communication in medical format (DICOM). For longitudinal evaluation of parotid gland volumes, the CT scans were categorized into 6 periods, periods 0, 1, 2, 3, 4 and 5, representing the timing of CT scans at 0–6 months, 7–18 months, 19–30 months, 31–42 months, 43–54 months, and 55–66 months after completion of IMRT.

Two radiation oncologists with 5 years and 15 years of clinical experience contoured the parotid glands on a three-dimensional radiation therapy planning system and measured and recorded the parotid gland volumes.

Measurement of the degree of moisture in the mouth and QOL evaluation

We assessed xerostomia 3 years or more after IMRT by measuring the degree of moisture in the mouth using a moisture-checking device (Mucus, Life Co., Ltd.) and oral QOL evaluation by GOHAI (General Oral Health Assessment Index).

The degree of moisture in the mouth was measured 3 times continuously by placing the moisture-checking device at the center of the tongue, and the average value of the 3 measurements was used as the measured value. Patients were instructed not to eat, drink or gargle for at least 30 minutes before the measurements and to rest for at least 5 minutes before the measurements. Measured values of the moisture-checking device were defined as follows according to a previous report [17]: <25, advanced drying; 25–28, moderate drying; 28–30, mild drying; 30 <, normal.

The GOHAI questionnaire is a questionnaire about the frequency of problems caused by a bad condition in the mouth during the past 3 months and consists of 12 questions. Five scales are used for answers and QOL is evaluated by the total score of 12 questions (with the lowest total score 12 and highest total score 60 and a higher the total score indicating higher quality of life) [17].

Statistical analysis

Statistical analyses were performed with SPSS 26.0. Since there were considerable individual differences in parotid gland volumes, the parotid gland volumes in each period were converted to the ratio to parotid gland volumes before radiotherapy (relative parotid volume). The Dunnett's test was used to evaluate the longitudinal changes in relative parotid volumes for periods 0–5. Using the Student's t-test, we compared the relative parotid volumes in each period for patients receiving less than 40 Gy with those for patients receiving 40 Gy or more and those for patients aged 50 years or younger with those for patients aged more than 50 years. Correlation analysis was performed for mean irradiated dose of the parotid, relative parotid volumes, measured values of the moisture-checking device and GOHAI score at the last observation date. For all analyses, $p < 0.05$ was considered statistically significant.

Results

Eligible patients' characteristics

Twenty patients were enrolled in this study (14 males and 6 females; median age, 52 years (range, 20–76 years)). In the T classification, 9 cases were T1, 6 cases were T2, 2 cases were T3, and 3 cases were T4, and in the N classification, 4 cases were N0, 9 cases were N1, 6 cases were N2, and 1 case was N3. Two cases were Stage I, 9 cases were Stage II, 5 cases were Stage III, and 4 cases were Stage IV

(classified according to UICC TMN classification 7th edition). All patients received platina-based chemotherapy in combination with IMRT concurrently. The mean irradiated dose of 40 parotid glands in 20 patients was 40.7 ± 9.5 Gy. The patients' characteristics are shown in Table.

Parotid volumes

Forty parotid glands in 20 patients were analyzed. The parotid volume before radiotherapy was 30.6 ± 9.9 cm³ (mean \pm SD). The relative parotid volumes in periods 0, 1, 2, 3, 4 and 5 were $67.9 \pm 10.1\%$ (n = 40), $67.7 \pm 13.6\%$ (n = 40), $74.3 \pm 12.5\%$ (n = 40), $75.8 \pm 12.4\%$ (n = 40), $78.3 \pm 17.4\%$ (n = 30), and $75.3\% \pm 17.7\%$ (n = 32), respectively (Fig. 1). The relative parotid volumes were significantly shrunken by radiotherapy (Dunnett's test: $p < 0.0001$ for all periods). The nadir of the relative parotid volume appeared in period 0 and relative parotid volume had recovered significantly in period 3 and 4 (Dunnett's test: both $p < 0.05$). Although the differences were not statistically significant, periods 1, 2 and 5 also showed recovery of relative parotid volume from period 0. The relative volumes of parotid that were irradiated with less than 40 Gy as the mean dose in periods 0, 1, 2, 3, 4 and 5 were $67.9 \pm 9.2\%$, $69.1 \pm 13.7\%$, $75.0 \pm 12.9\%$, $77.3 \pm 12.6\%$, $79.7 \pm 17.8\%$ and $77.2 \pm 15.8\%$, respectively. The relative parotid volume that were irradiated with less than 40 Gy as the mean dose had recovered significantly in period 3, 4 and 5 (Dunnett's test: all $p < 0.05$). The relative volumes of parotids that were irradiated with 40 Gy or more as the mean dose in periods 0, 1, 2, 3, 4 and 5 were $67.9 \pm 11.2\%$, $67.6 \pm 12.8\%$, $72.9 \pm 10.9\%$, $73.1 \pm 11.3\%$, $74.6 \pm 14.1\%$ and $71.0 \pm 20.0\%$, respectively. The relative parotid volume with 40 Gy or more as the mean dose had not recovered significantly. Although there were no statistically significant differences in periods 1, 2, 3, 4 and 5 the relative volumes of parotids irradiated with less than 40 Gy were larger than those of parotids irradiated with 40 Gy or more (Student's t-test: $p = 0.162-0.499$) (Fig. 2).

Oral moisture and QOL score

In 16 of the 20 patients, the degree of moisture in the mouth was measured by a moisture-checking device and oral QOL was assessed by GOHAI at 62.1 ± 3.6 months (range, 55–66 months) after IMRT. Measurements could not be performed in the other 4 patients because they did not visit our hospital or they refused to undergo an examination. The mean measured value of the moisture-checking device was 26.9 ± 5.7 (range, 6.2–30.7). The mean GOHAI score was 52.1 ± 7.3 (range, 38–60). A correlation was found between GOHAI score and the values of moisture-checking device ($r = 0.566$, $p = 0.022$) (Fig. 3). A negative correlation was found between mean irradiated dose for bilateral parotids and the values of moisture-checking device ($r = -0.585$, $p = 0.017$) (Fig. 4). A negative correlation was also found between mean irradiated dose for bilateral parotids and GOHAI score ($r = -0.570$, $p = 0.021$) (Fig. 5). No significant correlation was found between relative parotid volume and measured values of the moisture-checking device ($r = 0.122$, $p = 0.665$). There was also no significant correlation between relative parotid volume and GOHAI score ($r = 0.343$, $p = 0.211$).

Discussion

In this study, longitudinal changes in parotid gland volume were analyzed in patients with nasopharyngeal cancer who were treated by IMRT with chemotherapy, and the relationships of mean irradiated dose for the parotid with parotid gland volume and xerostomia symptoms were assessed. It was found that the parotid volume decreased rapidly during and immediately after radiotherapy and then recovered gradually and reached a plateau about 2 years after radiotherapy. We also found that the mean irradiated dose for bilateral parotids dose showed negative correlations with objective and subjective xerostomia symptoms after a long period. There have been few reports on long-term changes in the parotid after radiotherapy for head and neck cancer. To the best of our knowledge, there have only been two reports on long-term changes in parotid volume after radiotherapy for head and neck cancer. Tomitaka et al. evaluated parotid volumes at 2 weeks and 6, 12, and 24 months after radiotherapy in 15 patients who received 30 Gy /15 fr. as preoperative radiotherapy with opposed lateral fields for advanced oral cancer, and they reported that the parotid volumes decreased, reached a nadir at 6 months after radiotherapy, and had recovered at 24 months after radiotherapy [18]. They also reported that there was a correlation between decreased parotid volumes and decreased saliva production immediately after preoperative radiotherapy for patients with advanced oral squamous cell carcinoma [19]. Their results are consistent with our results; however, patients treated with radical radiotherapy or with IMRT were not included in their study. Chun et al. evaluated parotid volumes within 100 days, between 100 days and 1 year, and more than 1 year after radiotherapy in 11 patients with nasopharyngeal cancer who were treated by IMRT with 70 Gy / 35 fr., and they reported that the nadir of parotid volume was within 100 days and that the parotid volume was recovered more than 1 year after radiotherapy [20]. Their results are also consistent with our results; however, the observation period in their study was not sufficient. In our study, we analyzed longitudinal changes in parotid volumes for 3–5 years after radiotherapy. The present study is the first study in which long-term changes in parotid volume after radiotherapy for patients with head and neck cancer and the relationships of parotid volumes with subjective and objective xerostomia symptoms were investigated. Hey et al. reported that most of the recovery process from radiation-induced salivary gland injury was completed within 36 months after radiotherapy [16], and their results are almost consistent with the results of our study. Our data for parotid volumes 2 years and more after radiotherapy suggest that there is a relationship between radiation-induced salivary gland injury and parotid volumes. A relationship between parotid volumes and salivary flow has been reported. However, the correlation between oral moisture and QOL has not been shown, because observer-based monitoring of xerostomia symptoms could underestimate the actual xerostomia symptoms compared with patient-reported symptoms [21]. The present study is the first study showing the relation between parotid volume and oral QOL score 3 years or more after IMRT. And we showed the significant correlation between oral QOL score and measured values of the moisture-checking device; however, the correlation was not so strong. It might be because GOHAI score did not show only wetness in the oral cavity.

The parotid volumes decreased after radiotherapy and then recovered gradually and reached a plateau about 2 years after IMRT and there was no significant recovery thereafter. These results suggested that recovery from parotid volume reduction is mostly completed in about 2 years, as is recovery from

radiation-induced salivary gland injury. Although the mechanism of radiation-induced decrease in parotid volumes has not been elucidated, it was reported that the decrease in parotid volumes might be due to the loss of acinar cells or fibrosis and that the recovery of the parotid volumes might be due to regeneration of acinar cells [6, 20].

In this study, the relative volumes of only parotids receiving less than 40 Gy had recovered significantly after IMRT. Furthermore, the relative volumes of parotids receiving less than 40 Gy tended to be larger than those of parotids receiving more than 40 Gy in any periods except for immediately after IMRT, although there was no statistically significant difference. It suggested that mean irradiated dose for parotid gland should be suppressed less than 40 Gy. It is consistent with the past reports [22].

Both measured values of the moisture-checking device and GOHAI score were correlated with mean irradiated dose for bilateral parotids but were not correlated with relative parotid volume. This may also be due to the small number of patients. The functions and responses of the parotid glands are typically assumed to be uniform throughout the parotid gland, but they may not actually be uniform, and this may be the reason why there is no correlation between parotid volumes and function. Actually, there are reports that radiotherapy to the cranial half caused more functional loss than did radiotherapy to the caudal half in rats [23]. This is because saliva from the caudal part flows through the cranial part and is therefore affected by damage to the cranial part.

This study had some limitations. The number of eligible patients was only 20 and the number of patients in whom measurements by a moisture-checking device and evaluation of oral QOL were performed was only 16. Due to the small number of cases, there might have been some factors that were not clarified in the analysis. Since this study was a retrospective study and was performed only for patients for whom long-term follow-up was possible, the possibility of bias in selection of patients cannot be ruled out. In addition, although only parotid volumes were evaluated in this study, the irradiation field also included the submandibular gland, sublingual gland, and other salivary glands, and radiation-induced damage of salivary glands cannot be neglected for oral moisture or QOL. However, total saliva is mainly produced by the parotid gland, and radiation-induced injury to salivary glands mainly results from damage to parotid glands [1]. Therefore, we evaluated only parotid volumes in this study. Furthermore, we did not consider fatty change of the parotid after radiotherapy in this study.

Conclusions

The mean irradiated dose for the parotid should be reduce as much as possible to improve oral QOL long after IMRT.

Abbreviations

IMRT
intensity-modulated radiotherapy

3D-CRT

3D-comformal radiotherapy

QOL

quality of life

CTV

clinical target volume

PTV

planning target volume

GOHAI

General Oral Health Assessment Index

Declarations

Ethics approval and consent to participate

This research was approved by institutional review board in our institution.

Consent for publication

Not applicable

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions

(1) conception and design or analysis and interpretation of data: ST, KJ, NT, TY, YI, KT and YS

(2) drafting of the manuscript or revising it for important intellectual content: ST, KJ and HM

(3) final approval of the version to be published: ST, KJ and NK

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Figures

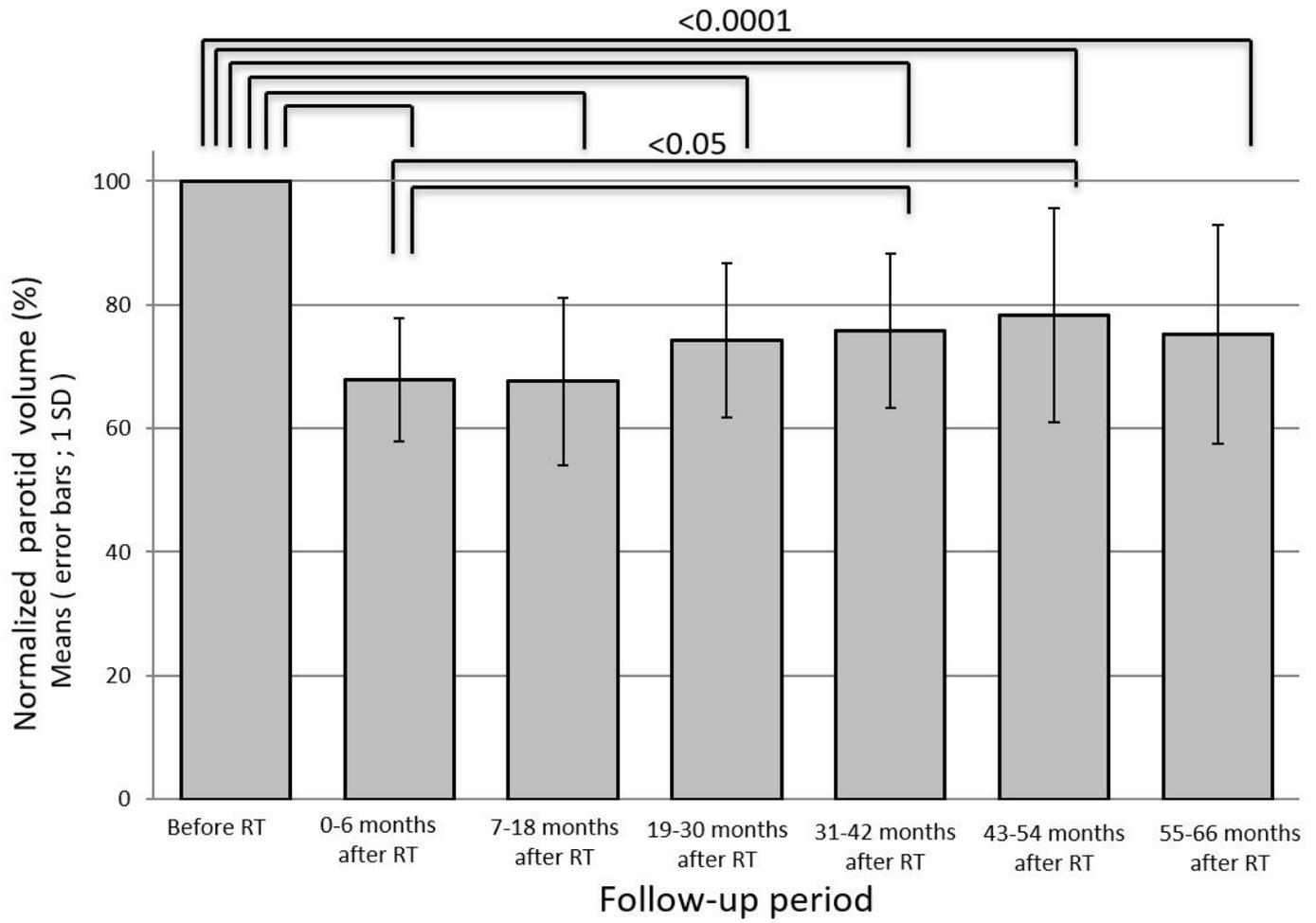


Figure 1

Longitudinal changes in relative parotid volumes after radiotherapy.

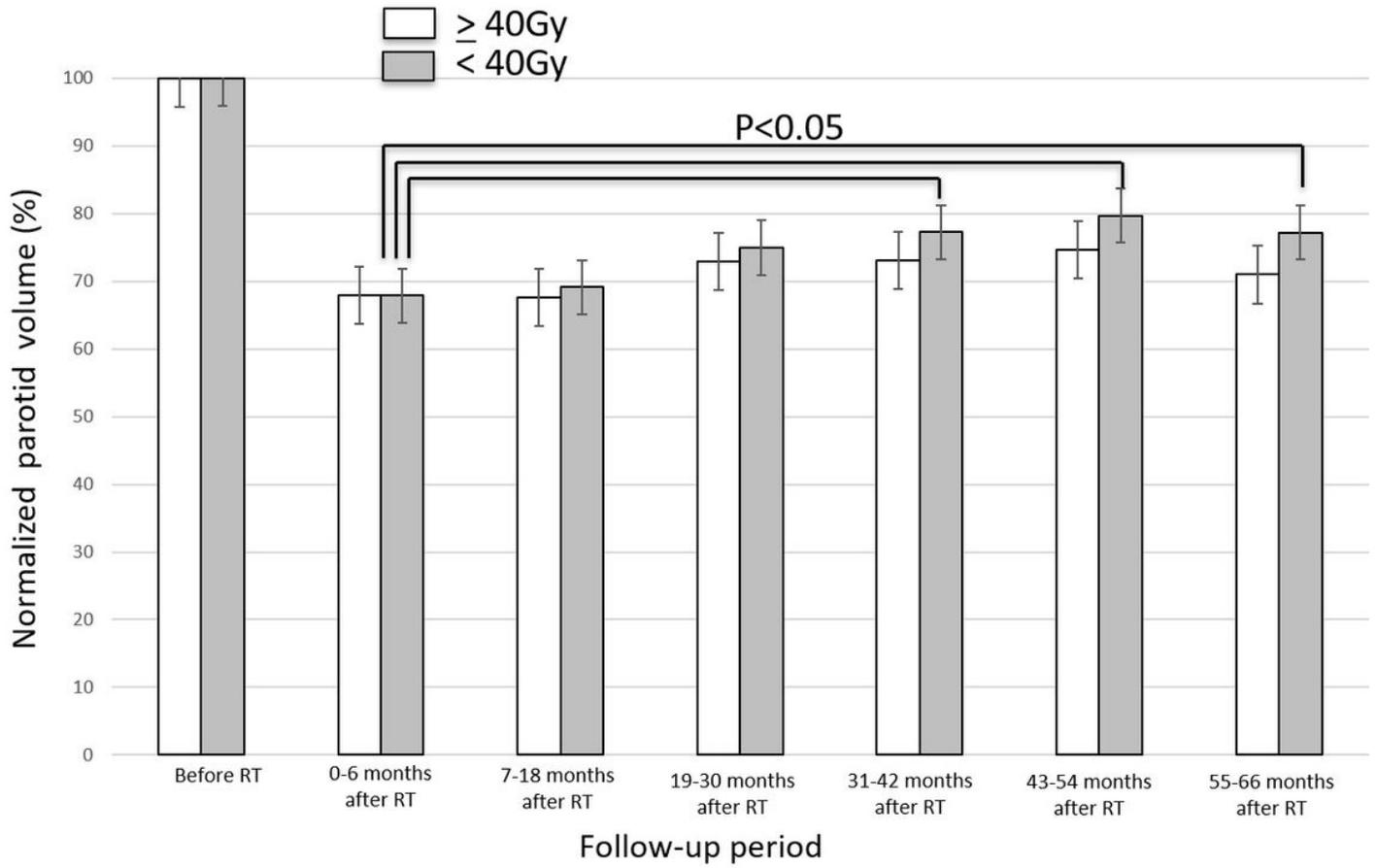


Figure 2

Longitudinal changes in relative parotid volumes after radiotherapy for parotids irradiated with less than 40 Gy and in parotids irradiated with 40 Gy or more.

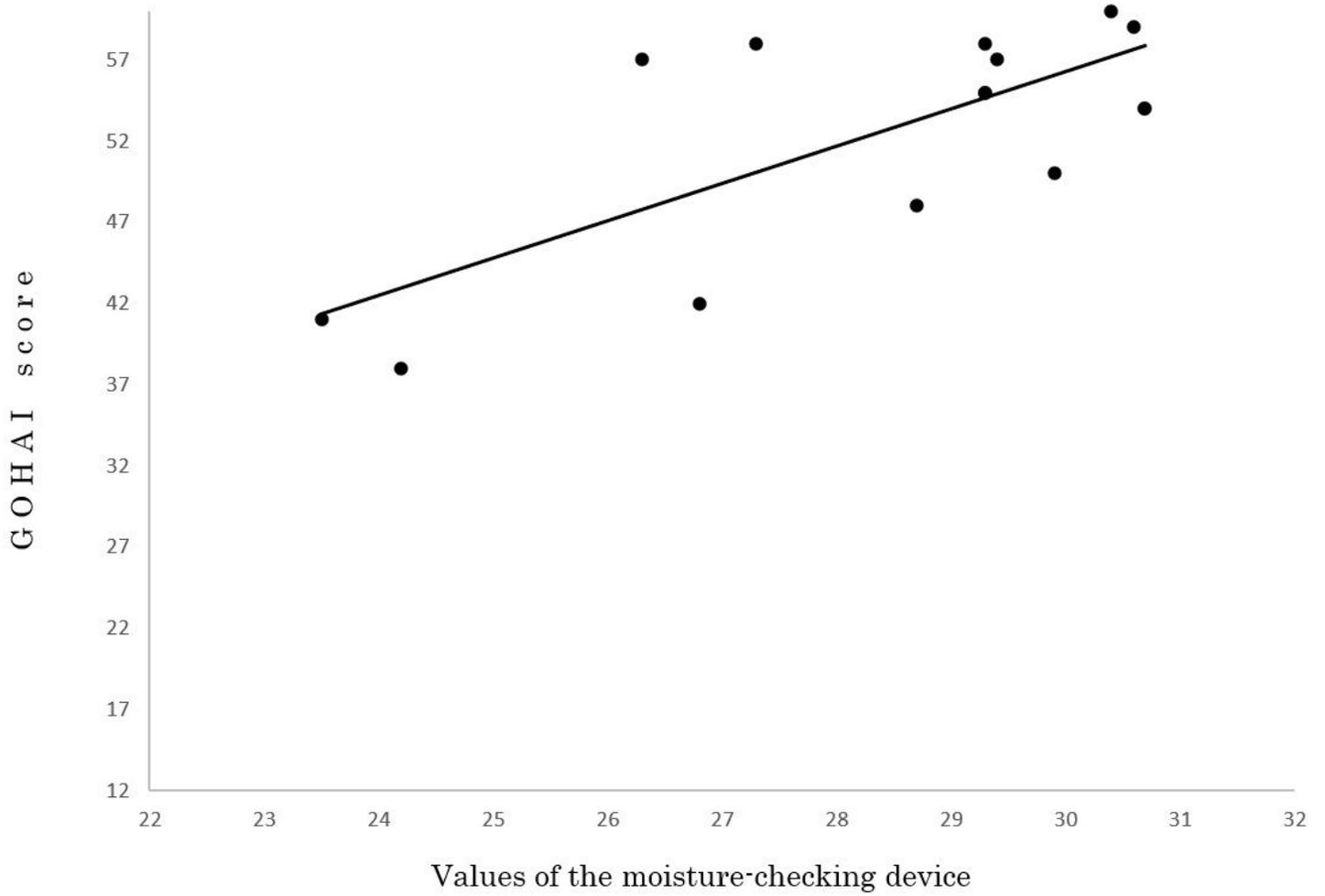


Figure 3

Correlation between GOHAI score and the values of the moisture-checking device.

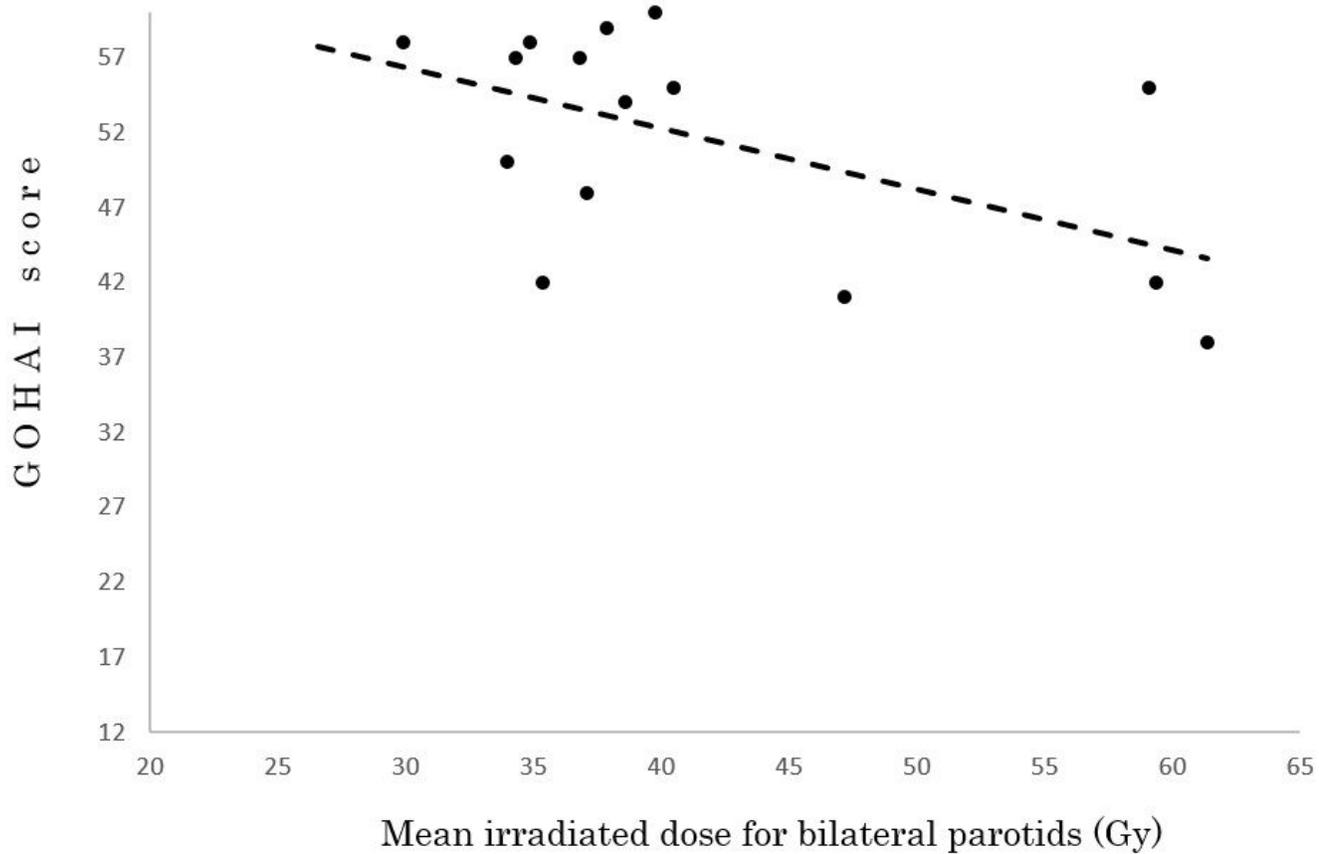


Figure 4

Correlation between mean irradiated dose for bilateral parotids and the values of the moisture-checking device.

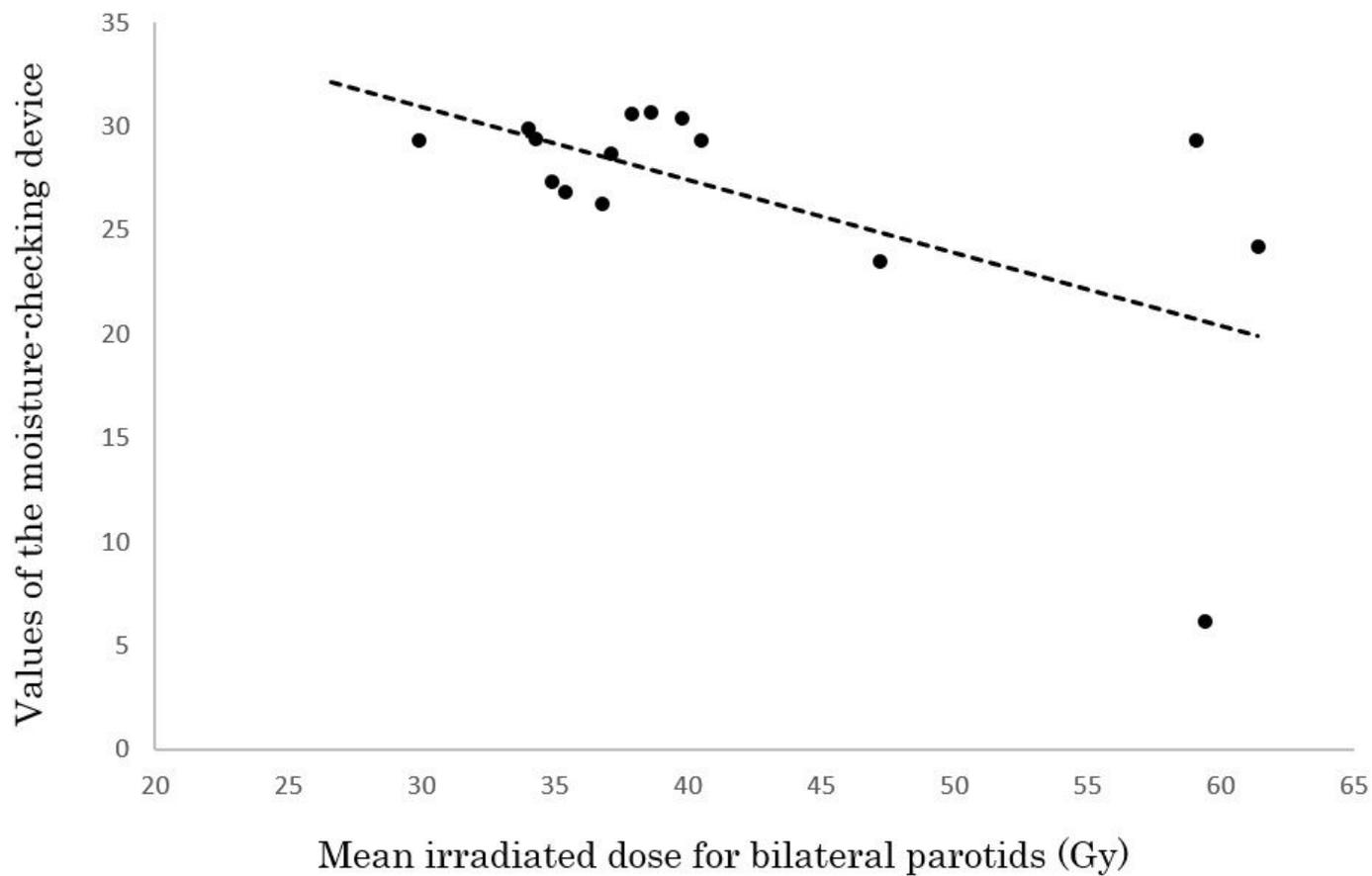


Figure 5

Correlation between relative parotid volume and GOHAI score.