Association Between Laryngopharyngeal Reflux and Radiation-induced Mucositis in Head and Neck Cancer

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Abstract. Background/Aim: We investigated whether laryngopharyngeal reflux (LPR) is a risk factor for radiation-induced mucositis. Patients and Methods: This was a retrospective cohort study using our departmental database. The study included patients with stage I or II laryngeal and hypopharyngeal cancers treated with radiation therapy alone between April 2009 and March 2014. Based on endoscopic findings, baseline laryngeal signs were evaluated using the reflux finding score (RFS), and the severity of mucositis was assessed during and after radiation therapy. Results: Fifty-eight patients were enrolled. Thirty-one patients were categorized as high RFS (LPR-likely), while 27 patients were categorized as low RFS (LPR-unlikely). Grade 3 mucositis occurred more frequently in the high RFS group (p<0.042). Furthermore, grade 3 mucositis developed earlier in the high RFS group (p<0.001). Conclusion: High RFS (i.e., increased likelihood of LPR) appears to be a potential risk factor for developing severe radiation-induced mucositis.

The management of radiation-induced mucositis is an important aspect of radiation therapy in head and neck malignancies. Severe mucositis leads to incomplete treatment, which is a critical problem, because completion of treatment is closely associated with survival and local control (1). Various methods have been attempted to treat radiation-induced mucositis (1, 2), such as the infusion of granulocyte-macrophage colony-stimulating factor (2, 3), L-glutamine administration (4), and usage of TJ-14 (or Hangeshashintou, a traditional Japanese medicine) (5). However, there is no evidence to date that any of these remedies are suitable for universal application (1, 2).

In the past few decades, a number of investigations have focused on the etiology and accurate diagnosis of laryngopharyngeal reflux (LPR), as well as its relationship to laryngeal cancer (6, 7). We speculated that, under chronic stress due to LPR, the laryngeal/pharyngeal membrane is more easily damaged by radiation. A previous report described two laryngeal cancer patients; these cases led us to postulate that a relationship exists between LPR and radiation-induced mucositis (8).

In this study, we hypothesized that LPR is a potential risk factor for developing severe radiation-induced mucositis. Moreover, we posited that the presence of LPR would accelerate the severity of radiation-induced mucositis. To that end, we conducted a retrospective cohort study of patients with stage I or II laryngeal and hypopharyngeal cancers who received radiation therapy as their primary treatment.

Patients and Methods

This study included patients with stage I or II laryngeal and hypopharyngeal cancers who were treated between April 2009 and March 2014. We enrolled patients who were listed in our departmental database as having received radiation therapy alone as the primary treatment; these patients were analyzed retrospectively. Patients were treated with radiation therapy of 64-72.3 Gy (mean 66 Gy at 2 Gy per fraction per day). Supraglottic cancer and hypopharyngeal cancer patients were also administered prophylactic irradiation (40-66 Gy, mean 46 Gy) to the bilateral neck regions. All but one hypopharyngeal cancer patient, who received intensity modulated radiation therapy, were treated with conventional radiation therapy. Patients who received chemotherapy before or during radiation therapy were excluded from the study.
The baseline laryngeal signs before the start of radiation therapy were evaluated using the reflux finding score (RFS; Table I). The severity of mucositis was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0; Table II) (9) based on weekly endoscopies, focusing mainly around the larynx and the hypopharynx. The CTCAE v3.0 was used because it allows retrospective assessment of mucositis based on endoscopic findings with fair objectivity. According to the previously described cut-off value (10), patients were divided into high (≥7) and low (<7) RFS groups, and the severity of mucositis was compared between the two groups. The baseline laryngeal signs and severity of radiation-induced mucositis were evaluated separately by two investigators, using the stored laryngoscopies from our departmental database. To eliminate measurement bias, the investigators had no contact with the enrolled patients and were blinded to each other’s evaluations.

The history of gastroesophageal reflux disease (GERD) was confirmed by information from other experts or by the findings of gastrointestinal fibrescopy conducted prior to radiation therapy. A history of proton pump inhibitor (PPI)/H2-blocker administration was defined as regular use of these drugs at any time before or during radiation therapy.

The primary endpoint of this study was the severity of radiation-induced mucositis. Mucositis of grade 3 (confluent ulcerations or pseudomembranes; bleeding with minor trauma) or higher was defined as “severe mucositis,” while mucositis of grade 2 or lower was defined as “mild mucositis.” The secondary endpoint was the time to development of grade 3 mucositis. The length of time between the start of radiation therapy and the date that grade 3 mucositis was detected was defined as “time to grade 3” (TTG3).

Univariate analyses using the Wilcoxon rank sum and Fisher’s exact tests were performed. The TTG3 was estimated using the Kaplan-Meier method. The effect of RFS (LPR) on TTG3 was compared using the log-rank test. Multivariate analysis was conducted using the Cox regression method. All statistical tests comparing the two groups were two-sided, and the 95% confidence interval was calculated. All statistical analyses were conducted with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (11).

The study protocol was approved by the ethics board of our institution. The study was performed in accordance with the Declaration of Helsinki and the ethical guidelines for medical research concerning humans of the Ministry of Education, Culture, Sports, Science, and Technology, Japan (12). The study protocol was posted on the website of our institution, and all patients were offered the opportunity to opt out of the study.

### Results

Fifty-eight patients were enrolled in this study. The baseline characteristics are listed in Table II. Thirty-one patients with
RFS ≥7 were assigned to the high RFS (LPR-likely) group, while 27 patients with RFS <7 comprised the low RFS (LPR-unlikely) group. Factors that may damage the laryngeal/pharyngeal membrane, as well as basic attributes such as age and sex, were compared between the high RFS (LPR-likely) and low RFS (LPR-unlikely) groups. No significant differences between the two groups were found with respect to these factors.

The relationship between RFS and grade 3 mucositis is shown in Table III. The rate of grade 3 mucositis was significantly higher in the high RFS (LPR-likely) group than in the low RFS (LPR-unlikely) group (41.9% versus 14.8%, \( p=0.042 \) (Fisher’s exact test)).

The Kaplan-Meier curve for TTG3 is shown in Figure 1. TTG3 was significantly longer in the low RFS (LPR-unlikely) group (\( p<0.001 \)). On multivariate analysis, which included all the variables listed in the baseline characteristics, only high RFS was shown to be a significant factor influencing the occurrence of grade 3 mucositis (hazard ratio=6.62, 95% confidence interval=1.58-28.0; \( p=0.01 \)).

**Discussion**

We showed that high RFS (i.e., high LPR likelihood) was a potential risk factor for developing severe radiation-induced mucositis. The incidence of grade 3 mucositis was significantly higher in the high RFS (LPR-likely) group. Furthermore, severe radiation-induced mucositis tended to occur earlier when RFS was high.

A previous report described that radiation-induced mucositis was successfully treated by PPIs, suggesting a link between LPR and radiation-induced mucositis (8). No other studies to date have explored the relationship between radiation-induced mucositis and either LPR or RFS. Our results suggest that high RFS may be a risk factor for developing severe radiation-induced mucositis.

There is much controversy regarding the etiology of LPR. It is believed to be an extension of GERD, but the correlation of the two diseases is still under discussion; one study showed that only 54% of patients with suspected laryngoscopic signs of GERD have abnormal esophageal acid exposure (13). LPR is thought to be caused by gastric acid induced-damage to the laryngeal/pharyngeal membrane, causing long-term adverse effects; however, recent studies suggest that pepsin may be responsible for the mucosal damage (14, 15). Regardless of the factors responsible, it is reasonable to hypothesize that radiation damages the mucosal membrane more severely when the membrane is under chronic stress due to LPR.

There are two limitations to our study. The first is the reliance on RFS for the diagnosis of LPR. The three main limitations include:

- The reliance on RFS for the diagnosis of LPR
- The lack of consideration of other potential risk factors
- The small sample size

Despite these limitations, our findings suggest that high RFS may be a risk factor for developing severe radiation-induced mucositis.
methods used to diagnose LPR are the reflux symptom index (RSI), pH monitoring, and RFS (7, 16). However, each has drawbacks, and there is currently no gold standard. As this study was retrospective, we were not able to obtain information on RSI and pH monitoring. The RFS has a sensitivity and specificity of 87.8% and 37.5%, respectively, in detecting pharyngeal reflux in patients diagnosed by pH monitoring (17). Although the advantage of RFS is its intra-rater consistency and objectivity (12), having an RFS ≥ 7 is not sufficient to diagnose LPR. Therefore, even though high RFS was found to be a risk factor for severe radiation-induced mucositis in our study, we could not readily conclude that LPR is responsible for this etiology. The second limitation is that assessment of mucositis in the hypopharyngeal area may not have been thorough in some cases. The modified Killian’s method allows for better observation of the hypopharynx (18); however, it has not been adapted for weekly endoscopy during radiation therapy. In our previous study, strong mucositis was observed in the perilaryngeal areas, including the postcricoid area (8). If the modified Killian’s method was performed in all cases, the frequency of grade 3 mucositis may have been higher, which may have influenced the results. A future prospective study that incorporates parameters such as RSI and pH monitoring, with more precise assessment of mucositis using the modified Killian’s method, may be warranted.

Conclusion

Our data suggest that high RFS may be a risk factor for developing severe radiation-induced mucositis. Moreover, we showed that severe mucositis tends to occur sooner in patients with high RFS. Since our results cannot readily conclude that LPR is a risk factor for developing severe radiation-induced mucositis, validation with additional studies is warranted.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

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