学位論文の要旨

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学位論文名	An Increase in *Fusobacterium* Is Associated with the Severity of Oral Mucositis After Radiotherapy
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論文内容の要旨

INTRODUCTION

Radiotherapy is commonly used for head and neck cancer. It frequently induces oral mucositis, which reduces quality of life and may interrupt treatment. The reported incidence of mucositis is high, and severe cases remain prevalent. Therefore, effective management is important, but current treatments such as analgesics, antiulcer agents, and antiseptics remain insufficient. The pathobiology of mucositis is complex, involving epithelial injury, inflammatory responses, and secondary bacterial colonization. Previous reports have suggested that alterations in the oral microbiota may contribute to the exacerbation of radiation-induced mucositis.

In recent years, 16S rRNA gene sequencing has enabled a comprehensive evaluation of the oral microbiota, including species that are difficult to culture by conventional methods. Several studies using this approach have reported changes in the oral microbiota during radiotherapy. However, consistent patterns have not been clearly established, and the relationship between specific bacteria and mucositis severity remains unclear.

This study aimed to analyze changes in the oral microbiota in patients undergoing radiotherapy for head and neck cancer using 16S rRNA gene sequencing and to identify bacteria associated with oral mucositis. Based on these findings, we sought to provide insights that may help inform the development of novel management strategies. Such strategies may include the use of targeted antibiotics or probiotics to control key pathogens.

MATERIALS AND METHODS

We conducted a prospective study of patients with head and neck cancer undergoing radiotherapy at Shimane University Hospital between January 2022 and December 2023. Patients receiving antibiotics or immunosuppressive agents at the time of enrollment were excluded. Oral rinse samples were collected before, during, and after radiotherapy. Oral mucositis was assessed weekly using the Radiation Therapy Oncology Group (RTOG) criteria, and patients were classified into a mild group with grade 0-2 or a severe group with grade 3 or higher. The oral microbiota was analyzed by 16S rRNA gene sequencing. Alpha diversity was assessed using the Chao1 and Shannon indices, and bacterial composition was evaluated at the genus level. Differences between the two groups were assessed using the Mann-Whitney U test, while multiple comparisons across the three time points of before, during, and after treatment were examined by the Steel-Dwass test. Correlations between relative abundances and mucositis severity were analyzed using Spearman's rank correlation.

The study protocol was approved by the Research Ethics Committee of Shimane University, and written informed consent was obtained from all participants.

RESULTS AND DISCUSSION

In total, 43 patients were analyzed. Before treatment, 15 genera showed an average relative abundance of $\geq 1\%$, including *Streptococcus, Prevotella, Veillonella, Rothia, Haemophilus, Fusobacterium, Neisseria, Porphyromonas, Gemella, Actinomyces, Granulicatella, Lactobacillus, Leptotrichia, Staphylococcus*, and *Lautropia.* After radiotherapy, a statistically significant decrease was observed in *Haemophilus, Neisseria, Lautropia*, and *Rothia* ($p < 0.05$). Alpha-diversity analysis demonstrated a significant increase in the Chao1 index during and after radiotherapy ($p < 0.05$), whereas the Shannon index remained unchanged. These findings suggest that radiotherapy increases species richness without altering evenness, while reducing genera that are typically abundant in healthy individuals, indicating treatment-associated dysbiosis.

When patients were stratified by mucositis severity, samples collected after treatment showed significantly higher relative abundances of *Fusobacterium, Capnocytophaga,* and *Parvimonas* in the severe group ($p < 0.05$). The average relative abundance of *Fusobacterium* exceeded 7% in the severe group, making it the most abundant genus in this group. Analyses of the extent of change from before to after treatment confirmed greater increases in *Fusobacterium, Leptotrichia, Capnocytophaga,* and *Parvimonas* in the severe group ($p < 0.05$). Among these genera, *Fusobacterium* showed a more pronounced difference between the mild and severe groups. Spearman's correlation analysis further supported these findings, showing that mucositis severity was positively associated with the relative abundances after treatment of these genera ($p < 0.05$), with *Fusobacterium* exhibiting a relatively steeper trend than the others. Taken together, these results suggest that *Fusobacterium* may represent an important microbial factor contributing to mucositis exacerbation, consistent with its known pathogenic properties such as promoting inflammation.

In contrast, *Veillonella, Rothia,* and *Lactobacillus* were more abundant in the mild group ($p < 0.05$), and correlation analyses indicated that both *Veillonella* and *Lactobacillus* were negatively associated with mucositis severity. Among them, *Lactobacillus* is particularly notable because its known probiotic potential may suggest a protective role against severe mucositis.

CONCLUSION

Our findings indicate that changes in the oral bacterial flora, particularly an increase in *Fusobacterium*, are closely associated with the severity of radiotherapy-induced mucositis. These findings suggest that controlling *Fusobacterium* may be beneficial in preventing severe mucositis in patients with head and neck cancer undergoing radiotherapy. Further research should focus on targeted approaches to manage the oral microbiome, aiming to improve patient outcomes through effective prevention of mucositis